

Complete revascularization of multivessel coronary artery disease in patients with ST elevation acute coronary syndrome – for whom and when?

A comprehensive review

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Atherosclerosis is the most common cause of coronary steno-occlusive disease and acute myocardial infarction is the leading cause of death in industrialized countries. In patients with acute ST elevation myocardial infarction (STEMI), there is unquestionable evidence that primary percutaneous coronary intervention providing recanalization of the infarct related artery (IRA) is the preferred reperfusion strategy. Nevertheless, up to 50% of patients with STEMI have multivessel coronary artery disease defined as at least 50% stenosis exclusive of IRA. There is conflicting data regarding the optimal treatment strategy and timing in such patients. Currently, it is assumed that stable patients might benefit from complete revascularization particularly in reducing the need for future unplanned procedures but only culprit lesion should be treated during index procedure in unstable patients. In this article, we provide a comprehensive overview of this important and currently highly debated topic.

Key words: atherosclerosis, acute ST elevation myocardial infarction (STEMI), multivessel coronary artery disease (CAD), infarct related artery (IRA), complete revascularization, coronary flow, fractional flow reserve (FFR)

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INTRODUCTION

Atherosclerotic diseases, including stroke and acute coronary syndromes, are the leading causes of both mortality and disability in industrialized countries¹. Although atherosclerosis itself is a relatively benign process of slow (lifelong) but gradual vascular remodeling, it may be abruptly complicated by rupture or erosion of an atherosclerotic plaque with an overlying thrombosis precipitating an acute ischemic event. In the event of acute and complete interruption of the major coronary artery flow an ST elevation myocardial infarction (STEMI) develops leading to transmural scarring with subsequent decrease of cardiac output. It is well documented that the majority of acute coronary events (in absolute numbers) are caused by rupture or erosion of hemodynamically non-significant atherosclerotic plaques, simply because these largely outnumber hemodynamically flow-limiting stenoses². Since atherosclerosis is a diffuse process, one is not surprised that up to 50% of patients evaluated for STEMI have multivessel coronary artery disease (CAD) universally defined as $\geq 50\%$ stenosis of at least one major epicardial non-infarct related artery (IRA) (Fig.1) (ref.^{3,4}).

ISCHEMIC BURDEN

Nowadays, atherosclerosis is viewed as an inflammatory disease and experiments with dietary modulation performed in the early 20th century have clearly proven

cholesterol to play a key role in promoting atherosclerosis⁵. It has also become evident that plaque progression is not a gradual process but rather a series of clinical injury and healing episodes. This concept is supported by pathological findings of distinct plaque laminations clearly demonstrating stepwise plaque progression. These “crises of inflammation” are dispersed over the arterial tree suggesting a diffuse effect of risk factors⁶. Thus, in patients with symptomatic stable CAD, the primary goal is to evaluate the extent of ischemia, because the greater the myocardium is at risk, the more pronounced the benefit from revascularization is⁷. Based on the individual pre-test probability, either non-invasive stress tests and imaging methods or selective coronary angiography may be performed with the latter allowing us to localize and visually estimate the significance of stenoses as well as to provide immediate treatment. However, the specificity of selective coronary angiography in determining the significance of CAD in patients with “grey-zone” 50–90% stenosis has been repeatedly questioned⁸. Fractional flow reserve (FFR) has emerged as an invasive technique for evaluating the hemodynamic relevance of coronary stenosis by means of the measurement of the relative poststenotic pressure drop during maximal coronary vasodilation (Fig. 2). Currently, it is considered the most direct way to assess the hemodynamic significance of individual coronary lesions and is recommended in all patients with borderline stenosis without non-invasive measurement of the extent of ischemia⁹. In addition to evaluating the ischemic burden, it is also relevant to keep the causal

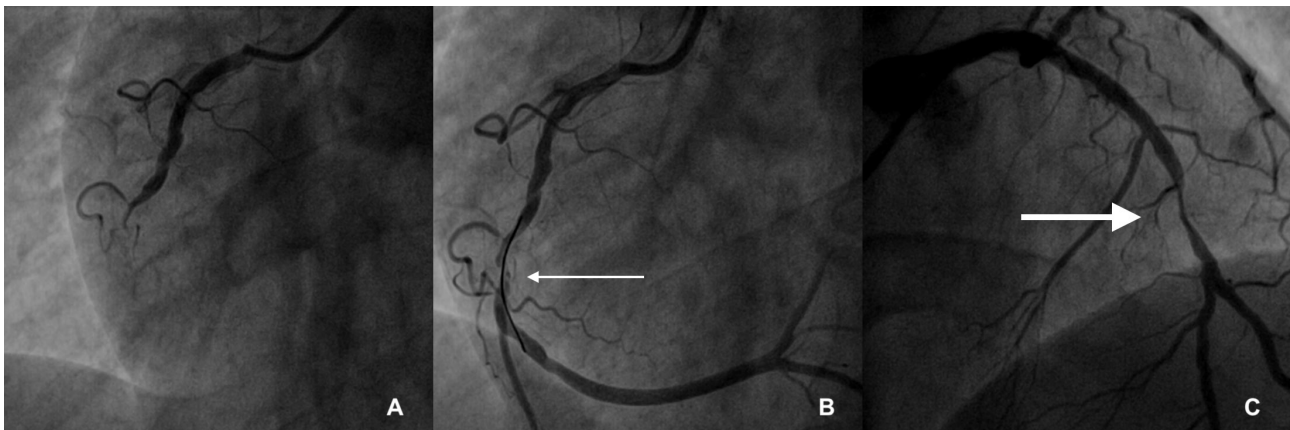


Fig. 1. Selective coronary angiography of a 54-year old patient presenting with inferior STEMI. A. Initial visualization revealing an acute thrombotic occlusion of the right coronary artery (middle segment). B. Crossing of the occlusion with a guidewire. C. Same patient's selective coronary angiography of the left coronary artery revealing significant stenosis in the middle segment of the left anterior descending coronary artery (thick arrow).

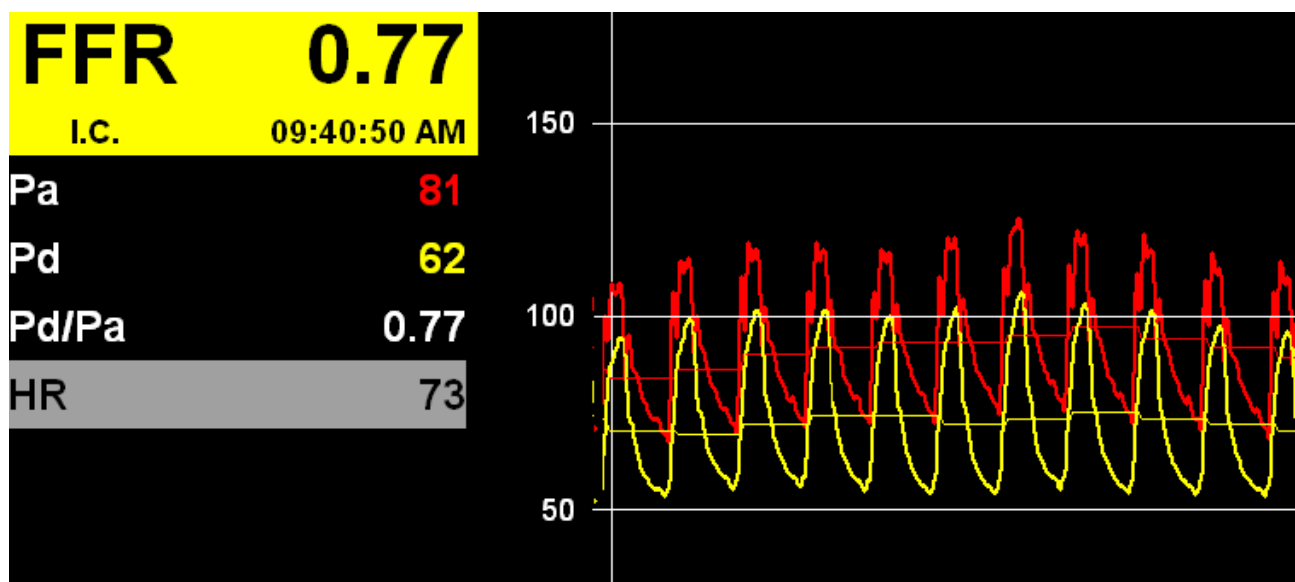


Fig. 2. Schematic FFR measurement diagram – comparison of mean aortic pressure (Pa – measured via guiding catheter) and mean poststenotic pressure (Pd – distal, measured with intracoronary FFR wire) during maximal vasodilation. A Pd/Pa value of 0.77 indicates hemodynamically significant stenosis (cutoff ≤ 0.80).

role of inflammation and the potential vulnerability of the plaque in mind. There are several markers suggesting the increased risk of plaque destabilization (Table 1) that may be evaluated using both non-invasive imaging as well as intracoronary imaging¹⁰. Consistent with these findings, it has been demonstrated that diabetic patients have more pronounced signs of plaque vulnerability, and patients with poorly controlled diabetes tend to have the most complex and diffuse CAD (ref.¹¹). Importantly, several studies have shown differences in plaque characteristics between patients with an acute coronary syndrome and stable CAD. In the former, non-IRA tend to have more high-risk features like less calcified plaques with thin-cap fibroatheromas and a higher percentage of lipid core, which makes them more prone to rupture^{12,13}.

Table 1. Morphological markers of plaque vulnerability.

positive vessel remodeling (dilation of the vessel wall to maintain sufficient lumen diameter)
presence of spotty calcifications
lower plaque density (related to the extent of lipid core or even plaque hemorrhage)
overall plaque volume
thin fibrous cap
intraplaque hemorrhage
plaque ulcerations
intraplaque neovascularization

COMPLEXITY OF THE MANAGEMENT STRATEGY

Considering the complexity of CAD, one can in theory simplify the management goals into 1) estimating the coronary vulnerability (“high-risk plaque”), and 2) evaluating the ischemic burden (“high-risk territory”). Despite the vast data in the literature, evaluation of plaque vulnerability requires advanced imaging and has thus far not been implemented in routine clinical practice as well as individual patient evaluation. In this regard, the maximum effort in plaque stabilization is universally “covered” with intensified lipid-lowering therapy, which is considered to be a cornerstone of CAD prevention as well as progression management¹⁴. Indeed, it has been reported that intensive lipid lowering therapy may stabilize the plaque¹⁵⁻¹⁷.

Like poor prognosis in patients with stable but extensive CAD, it has been clearly demonstrated that patients with STEMI and extensive CAD in vessels remote from the IRA have lower rates of ST segment recovery and an adverse prognosis following primary percutaneous coronary intervention (PCI) (ref.³). However, several early observational trials suggested an increase in adverse events, including mortality, in patients treated with immediate multivessel revascularization versus IRA PCI only¹⁸⁻²⁰. Even if these retrospective analyses may be limited by confounding (as sicker patients could be more likely to undergo more aggressive intervention at the time of PCI), the European Society of Cardiology (ESC) guidelines on Myocardial Revascularization 2014 recommend primary PCI for the culprit vessel, but revascularization of additional lesions in the case of cardiogenic shock only, as such patients were excluded from analysis²¹. Since the PCI technology has improved significantly over time decreasing the risk profile of more complex interventions, it has become important to evaluate the benefits and risks of complete revascularization in STEMI patients.

EVIDENCE BASED APPROACH

The Hepacoat for Culprit or Multivessel Stenting for Acute Myocardial Infarction (HELP AMI) study published in 2004 was one of the first randomized controlled trials to show that multivessel PCI was safe without any economic disadvantage²². Overall, 69 patients with STEMI undergoing primary angioplasty <12 h after symptom onset and with documented multivessel disease were included with approximately 2.3 lesions treated in the complete revascularization group (52 patients according to unbalanced randomization). The authors, however, concluded that if the culprit lesion was initially treated alone, the need for subsequent clinically driven revascularization remained low with no significant clinical advantages obtainable with a more aggressive initial approach over the 12-month follow-up period. It was recommended that a staged approach be preferentially used in order to avoid unnecessary treatment of clinically non-relevant lesions.

In 2010, a larger scale randomized controlled trial by Politi et al. was published²³. In this study the outcomes

of 263 patients with STEMI and multivessel CAD undergoing PCI were observed over a mean follow-up of 2.5 years. Before the first angioplasty, patients were randomly assigned to three different strategies: 1) culprit vessel-only, 2) staged revascularization, and 3) simultaneous treatment of non-IRA lesions. In the culprit vessel-only PCI group, 42 patients (50%) experienced major adverse cardiac event (MACE) compared to 13 patients (20%) in the staged revascularization and 15 patients (23.1%) in the simultaneous complete revascularization group. The authors concluded that culprit vessel-only angioplasty was associated with the highest rate of long-term MACE compared with multivessel treatment and that patients scheduled for staged revascularization experienced a similar rate of MACE to patients undergoing complete simultaneous treatment of non-IRA. It is, however, important to point out that the rate of MACE was driven by unplanned revascularizations or hospitalizations and the mean time between the first and the unplanned procedure was 42.3 ± 22.8 days. After this study, four randomized clinical trials have compared PCI of the IRA only vs. complete revascularization with subsequent impact on the update of ESC guidelines on STEMI published in 2017 (ref.²⁴). Table 2 provides a simplified overview of major randomized controlled trials comparing culprit-only to complete revascularization in acute STEMI patients.

In Preventive Angioplasty in Acute Myocardial Infarction (PRAMI) a total of 465 patients were evaluated and culprit vessel-only PCI (n=231) and immediate multivessel PCI (n=234) compared (ref.²⁵). The indication for non-IRA PCI was angiography-guided in lesions with $\geq 50\%$ stenosis. Recruitment was prematurely stopped by the data and safety monitoring board because of highly significant between group differences in favor of preventive PCI. The primary composite endpoint, consisting of death from cardiac cause or non-fatal myocardial infarction or refractory angina was significantly reduced after multivessel PCI during a mean follow-up time of 23 months. The absolute risk reduction was evident within 6 months and maintained thereafter. There was no difference concerning all-cause mortality between the two groups.

Another angiography-driven trial focusing on preventive PCI in STEMI is the Complete versus Lesion-only Primary PCI (CvLPRIT) trial, overall including 296 patients with >70% non-IRA stenosis²⁶. The complete revascularization group included 150 patients with non-IRA PCI performed during hospital stay (either during primary PCI (64%, recommended) or before discharge). The primary outcome of MACE (all-cause mortality, recurrent myocardial infarction, heart failure, ischemia-driven revascularization) was significantly reduced in favor of preventive PCI with early divergence and continuing separation of groups during the mean 12-month follow-up. There were no differences in the occurrence of serious adverse events between the two groups.

In The Third Danish Study of Optimal Acute Treatment of Patients with STEMI: Primary PCI in Multivessel Disease (DANAMI-3 PRIMULTI), 627 STEMI patients with multivessel CAD were randomly assigned to undergo

Table 2. Overview of major randomized controlled trials comparing culprit-only to complete revascularization in acute STEMI patients.

Trial	Inclusion period	Culprit only (n)	Complete - index (n)	Complete - staged (n)	Lesion criteria	Timing of complete revascularization	Primary endpoint	Follow-up period - months (mean)	Outcome(s)
Politi et al.	2003-2007	84	65	65	$\geq 70\%$ in ≥ 2 non-IRAs	Index complete, or planned staged (on average 56.8 ± 12.9 days after the primary PCI)	MACE: all-cause death, re-infarction, re-hospitalisation for acute coronary syndrome and repeat coronary revascularization	30	63% relative risk reduction of MACE after immediate complete revascularization, 60% after staged revascularization
PRAMI	2008-2013	231	234	0	$\geq 50\%$	Immediate only	Composite: death from cardiac cause, myocardial infarction, refractory angina	23	65% relative risk reduction in primary endpoint due to complete revascularization, no significant difference in death
CvLPRIT	2011-2013	146	97	42	$\geq 70\%$	Immediate (recommended) or during index admission	MACE (all-cause mortality, myocardial infarction, heart failure, ischemia-driven revascularization)	12	55% relative risk reduction in primary endpoint in the complete revascularization group, no significant difference in death
DANAMI-3 PRIMULTI	2011-2014	313	0	314	$\geq 90\%$ or $\geq 50\%$ + FFR ≤ 0.80	Staged FFR guided before discharge (2 days after index procedure)	Composite: all-cause death, myocardial infarction, ischemia-driven revascularization	27	44% relative risk reduction in primary endpoint due to reduction in ischemia-driven revascularization in complete revascularization group
COMPARE ACUTE	2011-2015	590	246	49	$\geq 50\%$ + FFR ≤ 0.80	Immediate or before discharge	Composite: all-cause mortality, myocardial infarction, any revascularization, cerebrovascular events	12	65% relative risk reduction of primary endpoint in complete revascularization (revascularization driven)
COMPLETE	2013-2017	2025	1420	596	$\geq 70\%$ or 50-69% + FFR ≤ 0.80	Index during hospital admission or staged after discharge (no later than 45 days after randomization)	Coprimary outcomes: First: death or myocardial infarction; Second: death, myocardial infarction or ischemia-driven revascularization	36	26% relative risk reduction in first coprimary outcome and 49% relative risk reduction in second coprimary outcome

primary PCI-only (313 patients) or staged complete FFR guided PCI (314 patients) before discharge²⁷. An FFR value ≤ 0.80 was considered hemodynamically significant and complete revascularization was performed a median of 2 days after initial PCI. After a mean follow up of 27 months, the primary combined endpoint of all-cause mortality, re-infarction and ischemia-driven revascularization was significantly reduced in the staged FFR-guided complete revascularization group, mainly driven by a 69% reduction of repeat revascularization of the non-IRA. There was no difference concerning all-cause mortality and non-fatal re-infarction.

Finally, the Comparison Between FFR Guided Revascularization Versus Conventional Strategy in Acute STEMI Patients with MVD (COMPARE-ACUTE) trial randomized 885 patients in 2:1 fashion to receive either FFR-guided complete revascularization (295 patients) or culprit-only revascularization (590 patients) (ref.²⁸). Complete revascularization was performed in 83.4% of patients during primary PCI in lesions with FFR ≤ 0.80 . The primary endpoint was a composite of death, non-fatal myocardial infarction, any revascularization, and cerebrovascular events. At 12 months, there was a 12.7% absolute reduction in the primary outcome in patients randomized to FFR-guided PCI of non-IRAs. This was primarily driven by an 11.4% absolute reduction in revascularizations, with no difference in mortality and a numerical trend toward fewer non-fatal myocardial infarctions. In summary, the Compare-Acute trial provides further evidence that treatment of non-IRAs discovered during STEMI is beneficial, although the results suggest that the benefit is largely restricted to a reduction in need for future revascularization rather than "harder" outcomes such as death or myocardial infarction.

Based on this data, updated 2017 ESC guidelines on STEMI recommended that PCI of non-IRA lesions should be considered in STEMI patients with multivessel disease before hospital discharge²⁴. However, as the optimal timing of revascularization (immediate vs. staged) had not been adequately investigated, no recommendation in favor of immediate vs. staged multivessel PCI could be formulated.

RECENT UPDATES

Complete Revascularization with Multivessel PCI for Myocardial Infarction (COMPLETE) was a long-awaited large-scale trial published in 2019 (ref.²⁹). Overall, 4 041 patients with STEMI and multivessel CAD who received successful culprit lesion primary PCI were randomized over a 4-year period to either no further revascularization or complete revascularization of all further significant non-culprit lesions. The significance of the residual lesions was defined as either $\geq 70\%$ stenosis based on angiography or 50–69% stenosis with FFR value ≤ 0.80 . Revascularizations of non-IRA lesions were performed either during or after the index hospitalization. At a median follow-up of 3 years, there was a 2.7% absolute reduction in the coprimary outcome of cardiovascular death and

new myocardial infarction, as well as 7.8% absolute reduction in cardiovascular death, new myocardial infarction and ischemia-driven revascularization in the complete revascularization group. The outcome was consistent across both stratified groups (complete revascularization during the index hospitalization or within 45 days of randomization). Like previous smaller scale trials, the COMPLETE trial also did not include patients in cardiogenic shock, limiting generalizability to that population. In summary, the COMPLETE trial confirmed on a large sample that complete revascularization was associated with a reduction in "hard outcomes" as the primary outcome was cardiovascular death or myocardial infarction. Subsequently, it was recommended that complete revascularization of non-culprit lesions in STEMI patients be adopted in guidelines, particularly for patients with similar characteristics as those included in the trial³⁰. Nevertheless, the result was again primarily driven by the lower incidence of new myocardial infarction in favor of complete revascularization (5.4% vs. 7.9%), while the incidence of death from cardiovascular causes was 2.9% and 3.2%, respectively (hazard ratio, 0.93; 95% CI, 0.65 to 1.32).

Cardiogenic shock is a serious condition complicating acute myocardial infarction in 5–10% of patients and is associated with a short-term mortality of 40–50% (ref.²⁴). Up to 80% of patients suffering from cardiogenic shock have multivessel CAD, further increasing mortality in these patients³¹. A concept supporting the immediate complete revascularization approach has therefore long been favored, suggesting that the improvement of overall myocardial perfusion and, thereby, function may be beneficial²¹. The Culprit Lesion-Only PCI versus Multivessel PCI in Cardiogenic Shock (CULPRIT-SHOCK) trial randomly assigned 706 patients with acute myocardial infarction (both STEMI as well as non-STEMI) and multivessel CAD to either immediate complete or target vessel-only PCI (ref.³²). In the latter group, completion of revascularization was encouraged and performed on the basis of evaluation of symptoms of ischemia, FFR, non-invasive testing with consideration of clinical and neurological status. The baseline hypothesis was that culprit lesion-only PCI was superior in this population. The primary endpoint was a composite of death from any cause and severe renal failure leading to renal replacement therapy within 30 days. The primary endpoint was significantly lower in patients who had target vessel only PCI during the index procedure (43.3% vs. 51.6%). This difference was largely driven by a 7.3% absolute reduction in all-cause mortality. Of note is that 21.5% of patients randomized to culprit lesion-only revascularization subsequently underwent staged or urgent repeat revascularization. Thus, the authors concluded that the acute hazards of prolonged procedure time seem to outweigh any potential negative effects of repeat revascularization and that given the short duration of follow-up, further studies are needed to confirm the long-term stability of these results.

Finally, in 2021 Puymirat et al. published a large scale Multivessel PCI Guided by FFR or Angiography for Myocardial Infarction (FLOWER-MI) trial focusing on patients with STEMI (ref.³³). In this multicenter trial, they

randomly assigned patients with STEMI and multivessel CAD to receive complete revascularization guided by FFR or angiography ($\geq 50\%$ stenosis). The primary outcome was a composite of death from any cause, non-fatal myocardial infarction or unplanned hospitalization leading to urgent revascularization at 1 year. Interestingly, completion of revascularization was strongly recommended to be performed as early as possible. However, in routine daily practice the staged intervention for non-culprit lesion was used in more than 95% of the patients in each group, with the mean time delay between the intervention being 2.6 ± 1.4 days in the FFR-guided group and 2.7 ± 3.3 days in the angiography guided group. The mean number of stents used per patient for non-culprit lesions was 1.01 ± 0.99 in the FFR-guided group and 1.50 ± 0.86 in the angiography-guided group. Over the 12-month follow-up period, a primary outcome event occurred in 32 of 586 patients (5.5%) in the FFR-guided group and in 24 of 577 patients (4.2%) in the angiography-guided group. Death occurred in 9 patients (1.5%) in the FFR-guided group and in 10 patients (1.7%) in the angiography-guided group; non-fatal myocardial infarction in 18 (3.1%) and 10 (1.7%), respectively; and unplanned hospitalization leading to urgent revascularization in 15 (2.6%) and 11 (1.9%), respectively. Overall, the authors concluded that an FFR-guided strategy did not have a significant benefit over an angiography-guided strategy with respect to the risk of death, myocardial infarction, or urgent revascularization at 1 year.

CONCLUSION

Atherosclerosis is currently viewed as a dynamic inflammatory process with progression and healing episodes that may or may not clinically manifest depending on many factors. As it is a diffuse disease, a significant proportion of patients presenting with STEMI have residual stenosis in non-culprit territory. Moreover, it is well known that acute coronary syndromes manifest (in absolute numbers) more likely on non-significant vulnerable lesions. Thus, relevant prediction of future coronary events would require complex insight into coronary anatomy as well as coronary histology, with the latter not being routinely applied in current clinical practice. In addition, the situation is further complicated by the individual response to pharmacological interventions (bearing in mind its increasing potential). Over the past 2 decades, several studies have focused on the outcomes of patients with STEMI with multi-vessel CAD. To date, no such trial has shown significant mortality benefit, however, it has been statistically confirmed that completion of revascularization is particularly beneficial in lowering the need for future unplanned revascularizations. Whether a decision based on FFR provides better selection in STEMI patients and increases the benefit remains questionable. Finally, there is no concluding data suggesting the optimal timing of non-culprit lesion treatment. Under such circumstances, it is of utmost importance to discuss the benefits and risks

of treatment with individual patients while considering the limitations of the trials.

ABBREVIATIONS

CAD, Coronary artery disease; ESC, European Society of Cardiology; FFR, Fractional flow reserve; IRA, Infarct related artery; MACE, Major adverse cardiac event; PCI, Percutaneous coronary intervention; STEMI, ST elevation myocardial infarction.

Search strategy and selection criteria

We examined studies and articles from various resources (e.g. PubMed, MEDLINE). The search terms used included atherosclerosis, STEMI, multivessel CAD, non infarct related artery, complete revascularization, coronary flow, FFR. Citations from journals with high impact factors were given special weight. Only English language papers were reviewed.

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