

REVIEW

ST-Elevation Myocardial Infarction: Preventive Percutaneous Coronary Intervention in the Non-Culprit Vessel*

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KEY WORDS: *myocardial infarction;
primary percutaneous coronary
intervention; preventive PCI*

ABBREVIATIONS

CAD = coronary artery disease

FFR = fractional flow reserve

IRA = infarct related artery

MACE = major adverse cardiovascular
eventsMVD = multi-vessel (coronary artery)
disease

PCI = percutaneous coronary intervention

STEMI = ST-segment elevation
myocardial infarction*Correspondence to:*

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Manuscript received February 24, 2014;

*Revised manuscript received June 16,
2014; Accepted June 22, 2014*

ABSTRACT

Patients with ST-segment elevation myocardial infarction (STEMI) and multi-vessel coronary disease (MVD) have poorer outcomes after primary percutaneous coronary intervention (PCI) compared to those with one-vessel disease. Current STEMI guidelines recommend revascularization of the infarct related artery (IRA) only during primary PCI, while PCI for non-IRA lesions should be performed after objective evidence of residual ischemia. Evidence regarding the optimal management strategy for non-IRA lesions in STEMI patients with MVD has been limited and mainly based on retrospective, contradictory and probably biased data. The recently published PRAMI randomized study challenges the guidelines since preventive acute multi-vessel PCI for significant stenoses in non-IRAs has been associated with a reduction of major adverse cardiovascular events (MACE) compared to PCI limited to the IRA. A review of the literature and a discussion about the implications of PRAMI study regarding the optimal revascularization strategy for STEMI with MVD are presented herein.

INTRODUCTION

Primary percutaneous coronary intervention (PCI) is currently the reperfusion treatment of choice in acute ST-segment elevation myocardial infarction (STEMI).^{1,2} Due to the diffuse nature of the atherosclerosis among patients with STEMI 30% to 60% have multi-vessel coronary artery disease (MVD).^{3,4} Continuous advancements in interventional techniques and adjuvant antithrombotic treatment have led to significant improvement in primary PCI procedural success, but still patients with MVD have poorer outcomes compared to those with one-vessel disease.^{4,5} This can be explained by more diffuse coronary atherosclerosis, left ventricular dysfunction extending into the non-infarct zone and an increased systemic inflammatory response with endothelial dysfunction, vasospasm and impaired flow in non-culprit vessels.⁶⁻⁹

Current STEMI guidelines recommend revascularization of the infarct-related artery (IRA) only during primary PCI, while PCI of non-IRAs is not recommended.^{1,2} It is also stated that decisions about PCI of non-culprit lesions should be taken later and

* in part presented at the **Athens Cardiology Update 2014** meeting in Athens on April 11, 2014

Conflict of Interest: none declared

only guided by objective evidence of residual ischemia.¹⁰ Only for patients in cardiogenic shock may PCI be performed for all critical lesions of large epicardial coronary arteries as it could contribute to reduced border zone ischemia and improved survival.^{11,12} In addition, when more than one culprit lesions are suspected acute multi-vessel PCI might also be beneficial.³

**STEMI AND MVD:
STRATEGIES FOR NON-IRA LESIONS**

Current evidence on the optimal management of non-IRA lesions in STEMI patients is limited and mainly based on retrospective and probably biased data. Treatment strategies range from a conservative approach with primary PCI of only the IRA and subsequent optimal medical therapy unless recurrent ischemia occurs to an aggressive approach with treatment of all significant lesions in the acute phase of primary PCI. The mainstream approach stands between these two extremes and is the one of staged procedures with the IRA treated acutely and other lesions treated later during the hospital stay or within 30-60 days following discharge (Fig. 1).¹³ For the time being there are no definite scientific answers about their relative merits, while each approach has advantages and disadvantages (Table 1).¹⁴

The conservative approach makes sense and current PCI

guidelines recommend optimal medical treatment or ischemia-driven PCI of non-culprit lesions.¹⁵ As for patients with stable coronary artery disease (CAD) in case of intermediate lesions non-invasive ischemia tests and fractional flow reserve (FFR) measurements could guide additional revascularization procedures.^{15,16} However, the systemic inflammatory reaction following STEMI can increase protease activity and destabilize atherosclerotic plaques, which explains why recurrent thrombotic events tend to cluster shortly after and often involve lesions not responsible for the initial presentation.^{17,18} In this context complete revascularization, acutely or staged, may have advantages since plaque instability may not be limited to the IRA only. In patients with STEMI and MVD incomplete revascularization has been shown to be a strong and independent risk factor for death and major adverse cardiac events (MACE).¹⁹ To the contrary complete revascularization has been associated with better long-term prognosis.³

Especially, immediate revascularization may reduce the risk of recurrent events by limiting myocardial injury and consequent systemic inflammation, whereas revascularization after completion of an infarct does not generally confer such a benefit. On the other hand, a weakened fibrous cap alone does not suffice to precipitate plaque rupture and not all plaques that rupture have thin fibrous caps.²⁰ Furthermore, performing acutely multi-vessel PCI can result in stenting clinically irrelevant lesions, based simply on the “oculosten-

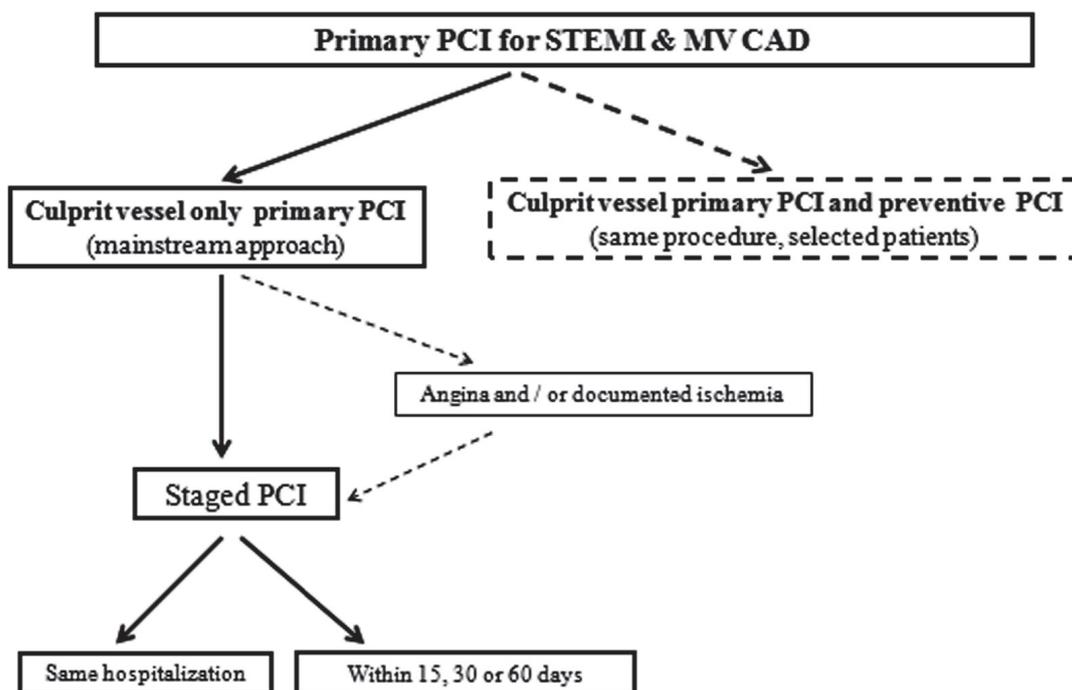


FIGURE 1. Current revascularization approaches for STEMI and MVD. MVD = multivessel (coronary artery) disease; STEMI = ST-elevation myocardial infarction.

TABLE 1. Advantages and disadvantages of different strategies for PCI revascularization in STEMI with multivessel (MV) coronary artery disease (CAD) regarding several issues (+: advantage, --: disadvantage).

	Acute MV PCI	IRA-only & ischemia driven PCI	IRA-only & staged PCI
Complete revascularization	+	--	+
Repeated procedures	+	--	--
Ischemia producing lesions	+	--	+
Multiple disrupted plaques	+	--	+
Double myocardial jeopardy	--	+	+
Stent thrombosis risk	--	+	+
Unnecessary stenting	--	+	+
PCI time, radiation, contrast	--	+	+
Risk/benefit assessment, Heart Team approach	--	+	+
Patient comfort	+	--	--
Hospital time/costs	+	--	--

otic” assessment of the operator without objective evidence of myocardial ischemia. To add complexity to the issue, Hanratty et al reported that 21% of lesions initially assessed as >50% during infarct angiography became <50% during angiography performed later.²¹ Moreover, Dambrink et al showed that infarct angiography overestimated the severity of non-culprit lesions and when FFR was performed it revealed that 40% of the non-culprit lesions did not show hemodynamic significance.²² Finally, important arguments against performing multi-vessel PCI acutely in STEMI are the augmented risk of additional PCI due to the pro-thrombotic and inflammatory milieu, the contrast load and the degraded left ventricular function in the acute phase. Any potential PCI complications in the non-IRA may lead to catastrophic consequences (double myocardial jeopardy) including peri-procedural death. In an observational study of STEMI patients undergoing PCI, the predicted probability of contrast induced nephropathy increased from 10.9% to 27.5% for patients with lowest to highest quartile of the contrast volume and patients who developed nephropathy had significantly higher in-hospital mortality.²³

Some of the abovementioned risks of acute multi-vessel PCI can be limited by staged procedures, which is currently the mainstream approach to obtain complete revascularization after primary PCI for STEMI.¹³ There are decades of possible scenarios based on combinations of angiographic and clinical findings in individual patients and decisions for revascularization often demand complex thinking and time. The advantage for staged PCI is that intervention on non-culprit lesions can be discussed within a Heart Team to determine the best individual management strategy.^{10,15}

ACUTE MULTI-VESSEL PCI DURING NON-SHOCK STEMI IN PRACTICE

Because on limited evidence different opinions exist on the use of acute multi-vessel PCI for STEMI across centers and operators. Whereas retrospective studies report unfavorable outcomes and guidelines discouraging acute multi-vessel PCI during non-shock STEMI, multi-vessel PCI remains relatively common in practice. A recent analysis of the National Cardiovascular Data Registry database found incidences of multi-vessel PCI in acute STEMI ranging between 0% and 38% among participating centers.²⁴ In the HORIZONS-AMI study 18.5% of patients underwent multi-vessel PCI but only 1.5% had cardiogenic shock.²⁵ In the APEX AMI trial, 9.9% of patients underwent multi-vessel PCI but only 1.0% was in Killip class IV (cardiogenic shock).²⁶ In the New York State Registry, 12.5% underwent multi-vessel PCI, but only 4.4% met the definitions of hemodynamic compromise.²⁷

The use of acute multi-vessel PCI in 10% to 20% of STEMI cases may be the result of two opposite clinical scenarios. Firstly, this aggressive strategy may be selected in an unfavorable setting. Non-culprit vessel PCI for critical lesions might be pursued even in hemodynamically stable patients in case of persisting chest pain and/or significant residual ST-segment elevation (Fig. 2). Identification and treatment of the culprit lesion is not always easy in patients with multi-vessel disease, especially in the presence of multiple critical lesions, small culprit vessels or total occlusions receiving collateral circulation. In some patients, a chronic occlusion may be attempted

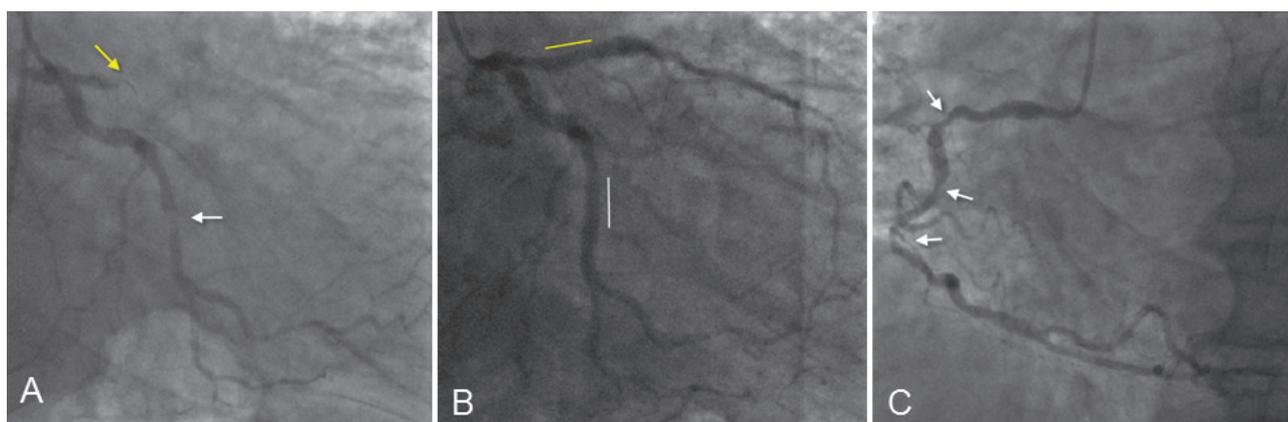


FIGURE 2. Example of a patient with 3-vessel coronary artery disease presenting with anterior STEMI and treated with acute multi-vessel PCI. After successful PCI of the left anterior descending artery it was necessary to treat a critical lesion of the marginal branch at the same procedure in order to stabilize the patient. The right coronary artery was not treated acutely despite consecutive significant lesions since angiographically they seemed stable and PCI in this tortuous artery would be complex. Staged PCI was performed 3 weeks later to complete revascularization. **A.** Before acute PCI. **B.** After acute PCI. **C.** Right coronary artery at initial presentation. PCI = percutaneous coronary intervention.

first and subsequently another vessel will be attempted when the error is recognized. It should not be forgotten that in some cases identifying a single culprit lesion in the presence of multi-vessel disease may be hampered by the variable ability of the electrocardiogram to localize infarctions.²⁸ All these factors may cause delayed or unsuccessful reperfusion and contribute to adverse prognosis. Alternatively, this strategy may be selected sometimes in a favorable setting where successful culprit vessel stenting has been readily accomplished during a smooth procedure. If another easy to treat target lesion is identified in this patient, the temptation to finish the procedure achieving complete revascularization might be high. Conversely, complex lesions requiring long procedures would discourage the operator to prolong the acute PCI after treating the IRA.

ACUTE MULTI-VESSEL PCI IN STEMI: THE LITERATURE

Existing data are somewhat conflicting and controversial (Table 2).

I) STUDIES SUPPORTING IRA-ONLY PCI

Several retrospective studies have demonstrated that multi-vessel PCI during the course of STEMI is harmful and thus support the conservative approach of IRA-only PCI in the acute STEMI phase.

Corpus et al described significantly higher risk of reinfarction (13% vs 2.8%, $p=0.001$), repeat revascularization (25% vs 15%, $p = 0.007$) and MACE (40% vs 28%, $p =$

0.006) with acute multi-vessel PCI (152 patients) compared to IRA-only PCI (354 patients).²⁹ Cavender et al examined the U.S. National Cardiovascular Data Registry from 2004 to 2007 to identify STEMI patients with MVD undergoing primary PCI.²⁴ In-hospital mortality of 3134 patients (10.8%) with acute multi-vessel PCI was compared with that of the remaining 25802 patients undergoing IRA intervention only. Patients with multi-vessel intervention during primary PCI were at higher risk and more likely presented in cardiogenic shock. Overall, the in-hospital mortality rate was higher in patients undergoing acutely multi-vessel PCI. The increased in-hospital mortality persisted after adjustment for potential confounders and surprisingly, even among patients presenting with cardiogenic shock.

Toma et al after a secondary analysis of the APEX-AMI trial found acute multi-vessel PCI to be performed only in 9.9% of patients with STEMI and multi-vessel disease. Ninety-day death and death/congestive heart failure/shock were higher in this group compared with the IRA-only PCI group (12.5% vs 5.6%, $p < 0.001$ and 17.4% vs 12.0%, $p = 0.02$, respectively). After adjusting for patient and procedural characteristics, as well as propensity for performing acute multi-vessel PCI, this procedure remained independently associated with an increased hazard of 90-day mortality (adjusted hazard ratio 2.44, $p < 0.001$).²⁶

II) STUDIES SUPPORTING IRA-ONLY PCI FOLLOWED BY STAGED PCI OF NON-IRAS

Data from several studies support staged PCI after IRA-only primary PCI, which is currently the mainstream approach to obtain complete revascularization after primary PCI for STEMI.¹³

TABLE 2. Studies that examine strategies for revascularization of non-culprit lesions in STEMI with MV CAD.

Studies	Year	Centers	Patients number			Comparison	Findings
			Number of patients with primary PCI and MV CAD	Acute MV PCI	Staged MV PCI		
Retrospective							
Corpus et al ²⁹	2004	Single-center	506	26	126	IRA-only PCI vs acute MV PCI vs staged PCI	MV PCI was an independent predictor of MACE at 1 year (odds ratio = 1.67, p =0.01).
Chen et al ³²	2005	Single-center	1384	202	37 within 1 week	IRA-only PCI vs acute MV PCI	MV PCI in patients with MV CAD after myocardial infarction (STEMI or non STEMI) compared with 1-vessel PCI was not associated with an excess risk of death or of combined death, myocardial infarction, coronary artery bypass graft, or target vessel revascularization.
Kong et al ³³	2006	Multi-center (NYSPCIRS)	1982	632		IRA-only PCI vs acute MV PCI	In-hospital mortality was three-fold lower (0.8 versus 2.3%, p=0.018) in the MV PCI group. After multivariate analysis, MV PCI remained a significant predictor of lower in-hospital death (odds ratio=0.27, 95% CI=0.08-0.90, p=0.03).
Rigattieri et al ³⁰	2008	Single-center	110		64: at index admission	IRA-only PCI vs staged PCI (at index admission)	Early MV staged PCI in STEMI patients is associated with a lower incidence of follow-up MACE but with a higher incidence of in-hospital MACE, mainly driven by periprocedural myocardial infarction during the elective procedures.
Varani et al ³⁴	2008	Single-center	399	147 (37%)	96 (24%): at index admission	IRA-only PCI vs acute MV PCI vs staged PCI (at index admission)	30-day mortality was 6.3% for IRA-only PCI versus 2.8% for MV PCI (p = 0.023), without differences if in acute (3.3%) or in staged sessions (2.2%).
Qwarawani et al ³⁵	2008	Single-center	120	95		IRA-only PCI vs acute MV PCI	Acute MV PCI was associated with reduced incidence of in-hospital MACE. In-hospital and one year mortality were similar.
Cavender et al ²⁴	2009	Multi-center (NCDR)	31681	3134 (10.8% after excluding staged PCI)	2745	IRA-only PCI vs acute MV PCI	The overall in-hospital mortality rates were greater in patients undergoing MV PCI (7.9% vs 5.1%, p <0.01). Even among patients with STEMI and cardiogenic shock (n = 3,087), those receiving MV PCI had greater in-hospital mortality (36.5% vs 27.8%, p<0.01).
Toma et al ⁶	2010	Multi-center (APEX-AMI trial)	2201	217 (9.9%)		IRA-only PCI vs acute MV PCI	Acute MV PCI was significantly associated with increased mortality.

TABLE 2. (continued) Studies that examine strategies for revascularization of non-culprit lesions in STEMI with MV CAD.

Studies	Year	Centers	Patients number		Comparison	Findings
			Number of patients with primary PCI and MV CAD	Acute MV PCI		
Hannan et al ²⁷	2010	Multi-center (NYSPCIRS)	4024	503	IRA-only PCI vs acute MV PCI vs staged PCI	IRA-only PCI was associated with lower in-hospital mortality than MV PCI during the index procedure (0.9% vs. 2.4%, p = 0.04). MV PCI within 60 days after the index procedure had a significantly lower 12-month mortality rate than patients undergoing IRA-PCI only (1.3% vs. 3.3%, p = 0.04)
Kormowski et al ²⁵	2011	Multi-center (HORIZONS study data)	668	275	Acute MV PCI vs staged PCI	Acute MV PCI versus staged PCI was associated with higher 1-year mortality, cardiac mortality, definite/probable stent thrombosis and a trend towards more MACE.
Jensen et al ³¹	2012	Multi-center (Western Denmark Heart Registry)	1174	354 (30.2%)	Acute MV PCI vs staged PCI	Acute MV PCI in patients with STEMI was associated with increased mortality.
Jaguszewski et al ³⁶	2013	Multi-center (Swiss Amis plus registry)	4941	1108 (22.4%)	IRA-only PCI vs acute MV PCI	In-hospital mortality after acute MV PCI was higher when compared with IRA-only PCI (7.3% vs. 4.4%; p < 0.001). When patients were stratified by risk: in-hospital mortality for acute MV PCI vs. IRA-only PCI was 2% vs. 2% (p = 1.00) in low-risk patients and 22.2% vs. 21.7% (p = 1.00) in high-risk patients.
Prospective						
Di Mario et al ³⁸	2004	Multi-center, randomized	69	17	Acute MV PCI vs staged PCI	A similar low incidence of in-hospital MACE was observed in the 2 groups.
Khattab et al ⁴⁰	2008	Single-center	73	28	Acute MV PCI vs staged PCI	Similar rates of MACE at one year were observed in the 2 groups.
Politi et al ³⁹	2010	Single-center, randomized	214	65	IRA-only vs acute MV PCI vs staged PCI	IRA-only PCI was associated with the highest rate of long-term MACE compared with MV PCI. Patients scheduled for staged PCI experienced a similar rate of MACE with patients undergoing acute MV PCI.
Wald et al ⁴⁴	2013	Multi-center, randomized.	465	234	IRA-only vs acute MV PCI	Preventive PCI in non-IRAs with major stenoses significantly reduced the risk of MACE, as compared with IRA-only PCI.

MV: multi-vessel; CAD: coronary artery disease; PCI: percutaneous coronary intervention; IRA: infarct-related artery; NCDR: National Cardiovascular Data Registry; NYSPCIRS: New York State's Percutaneous Coronary Interventions Reporting System.

In a small single-center study, Rigattieri et al found that in STEMI patients IRA-only PCI with subsequent medical treatment has better early outcomes, whereas early (same admission) staged multi-vessel PCI is associated with fewer MACE at follow-up (mean length: 13 months) at a cost of a higher incidence of in-hospital MACE, mainly driven by peri-procedural myocardial infarction during the elective procedure.³⁰

Based on the New York State PCI Registry, Hannan et al reported that in hemodynamically stable patients with MVD, acute phase multi-vessel PCI results in an increased in-hospital mortality when compared with IRA-only PCI (2.4% vs 0.9%, $p=0.04$). On the contrary, patients undergoing staged multi-vessel PCI within 60 days after the index procedure had a significantly lower 12-month mortality rate than patients undergoing IRA-only PCI (1.3% vs 3.3%, $p = 0.04$).²⁷ In a post-hoc cohort analysis of the HORIZONS-AMI trial, Kornowski et al reported that multi-vessel PCI was associated with a higher 1-year mortality (9.2% vs 2.3%) and stent thrombosis rate (5.7% vs 2.3%) than staged PCI.²⁵

Finally, based on data from the Western Denmark Heart Registry, Jensen et al examined mortality according to timing of multi-vessel PCI in a cohort of 1174 patients with STEMI and MVD.³¹ The adjusted hazard ratios for one-year mortality were 1.53 for acute multi-vessel PCI, 0.60 for staged procedure during the index hospitalization and 0.28 for staged procedure performed within 60 days, compared to patients with single vessel disease. Thus, acute multi-vessel PCI in patients with STEMI was associated with increased mortality, while staged procedures were associated with superior survival outcomes.³¹

III) STUDIES SUPPORTING ACUTE MULTI-VESSEL PCI

Some retrospective and small prospective studies suggest that acute multi-vessel PCI during STEMI could be beneficial and thus support such an aggressive approach.

In a single-center registry, Chen et al compared outcomes between patients with myocardial infarction (STEMI or non-STEMI) who underwent multi-vessel PCI within 7 days (239 patients; 202 in one procedure, 37 with staged procedures) and patients who underwent treatment of the IRA alone ($n = 1145$).³² The multi-vessel PCI group had a significantly higher prevalence of adverse prognostic indicators, yet the observed 1-year survival and event rates were similar between the two groups.³²

Kong et al analyzed patients undergoing PCI for STEMI (632 with multi-vessel PCI and 1350 with IRA only PCI) from the New York State Angioplasty Registry database (years 2000–2001). The highest risk patients (previous myocardial infarction, PCI, bypass surgery, or cardiogenic shock) were excluded. In-hospital mortality was lower (0.8% vs 2.3%, $p=0.018$) in the multi-vessel PCI group. No differences were observed in other ischemic complications, renal failure, or

length of stay. After multivariate analysis, multi-vessel PCI remained a significant predictor of lower in-hospital death (odds ratio = 0.27, $p= 0.03$).³³

In a small single-center registry, Varani et al found among 745 STEMI patients that acute multi-vessel PCI is feasible and safe. This study described the relative proportions of the three most frequently used strategies for revascularization in STEMI with multi-vessel disease: IRA-only primary PCI (39%), staged PCI (24%), and acute multi-vessel PCI (37%). Mortality at 30 days was 6.3% for IRA-only PCI versus 2.8% for multi-vessel PCI ($p = 0.023$), without differences if in a single (3.3%) or in staged session (2.2%).³⁴ In a similar small study, Qarawani et al reported a decrease in recurrent infarctions or ischemia but no survival benefit with acute multi-vessel PCI compared to IRA-only PCI.³⁵

Jaguszewski and colleagues recently analyzed the Swiss AMIS Plus registry for in-hospital outcome of patients undergoing single-vessel or multi-vessel PCI during the acute primary PCI procedure.³⁶ Rates of multi-vessel PCI were greater among the three categories of high-risk patients (out-of-hospital cardiac arrest, class Killip III/IV and left main involvement). Overall, in-hospital mortality after acute multi-vessel PCI was higher when compared with IRA-only PCI (7.3% vs 4.4%; $p<0.001$). However, this result was not present when patients were stratified by risk; in-hospital mortality for multi-vessel PCI vs IRA only PCI was 2% vs 2% ($p=1.00$) in low-risk patients and 22.2% vs 21.7% ($p=1.00$) in high-risk patients. Thus, one can conclude that acute multi-vessel PCI is not per se harmful compared to IRA-only primary PCI and that acute complete revascularization is potentially beneficial in reducing costs and being more patient-friendly.^{36,37}

Despite rigorous adjustments using complex statistics the abovementioned retrospective studies suffer from the potential for residual bias caused by unmeasured confounders. Some small prospective studies also challenge current recommendations and suggest that the strategy of acute multi-vessel PCI in STEMI could be beneficial.³⁸⁻⁴⁰ Di Mario et al in the HELP-AMI multi-center, randomized trial assigned 69 STEMI patients with multi-vessel disease to unbalanced randomization with culprit-lesion only and then staged PCI ($n = 17$) versus complete acute multi-vessel PCI ($n = 52$).³⁸ They found acute multi-vessel PCI to be safe despite requiring longer procedures and larger amounts of contrast, with a trend for lower revascularization requirements at 12 months and no economic advantages. They acknowledged, however, that the staged approach avoids treating lesions unnecessarily.³⁸ In a prospective single-center study, Khattab et al found no mortality benefit and no difference in MACE at one year with acute multi-vessel PCI compared to staged PCI.⁴⁰ In a more recent study, Politi et al randomized 214 STEMI patients with MVD to IRA-only PCI ($n = 84$), simultaneous treatment of non-IRA lesions ($n = 65$) or IRA-only PCI followed by staged revascularization ($n=65$). In-hospital mortality, unplanned

re-hospitalization and repeat revascularization occurred more frequently with the IRA-only PCI strategy which emerged as an independent predictor of adverse events.³⁹ Although the results of these prospective studies are provocative, they were significantly underpowered to detect differences in death or recurrent myocardial infarction. Furthermore, the requirement for repeat revascularization in case of the IRA-only PCI should not be considered a MACE, since a closer clinical follow-up is needed compared to the other approaches.

METANALYSES

Three meta-analyses of studies comparing preventive acute complete revascularization in STEMI to culprit-only primary PCI were published in 2011.^{6,41,42} The meta-analysis of Sethi et al analyzed 9 non randomized studies (including 31853 patients) and 2 small randomized studies that were added in secondary analysis. Long-term mortality and MACE were found similar for both strategies.⁴¹ A second meta-analysis by Bangalore et al included 19 studies (23 arms) that evaluated 61764 patients with STEMI and MVD similarly concluded that acute multi-vessel PCI appeared to be safe compared to culprit-only PCI.⁶ In the meta-analysis by Vlaar et al, which analyzed 14 retrospective and four prospective studies involving 40280 patients, the results of the large cohort studies seem to disagree with the results of smaller prospective studies.⁴² Pooled results of 9 retrospective cohort studies of 5128 patients suggested higher long-term mortality after acute multi-vessel PCI than after IRA-only PCI, whereas pooled results of 3 prospective studies of 288 patients suggested no difference. Pairwise meta-analyses demonstrated that staged PCI was associated with lower short- and long-term mortality as compared with IRA-only PCI and acute multi-vessel PCI and that acute multi-vessel PCI was associated with the highest mortality rates at both short- and long-term follow-up. In network analyses, staged PCI was also consistently associated with lower mortality.⁴² The results of the meta-analysis by Vlaar et al show that a staged PCI should be the preferred approach and appear to contradict the conclusions of the other two contemporary meta-analyses, which suggest no difference in long-term mortality rates after multi-vessel PCI or IRA-only PCI.^{6,41} These discordant findings could be attributed to methodological differences, which is a common phenomenon for meta-analyses conducted at about the same time by different investigators.⁴³

PRAMI STUDY: RESULTS AND COMMENTS

After considering the abovementioned published data one concludes that in STEMI with MVD the appropriateness of additional PCI procedures of apparently significant yet asymptomatic non-culprit lesions is highly debatable with only

limited and conflicting evidence. The most recently published randomized trial showed a significant reduction of MACE in the acute multi-vessel “preventive” PCI group compared to the IRA-only PCI plus optimal medical therapy group.⁴⁴ The objective of the Preventive Angioplasty in Myocardial Infarction trial (PRAMI) was to determine whether preventive PCI performed during the same procedure as the IRA PCI would be beneficial. A total of 465 consecutive patients with acute STEMI and MVD were enrolled in this randomized, multi-center, single-blind study. MVD was defined as >50% stenosis in one or more non-infarct arteries suitable for PCI. Patients were excluded in case of cardiogenic shock, prior coronary artery bypass graft surgery, >50% stenosis in either the left main or ostia of both the left anterior descending and circumflex arteries or if the only non-IRA stenosis was a total occlusion. The patients were randomized after successful emergency PCI to preventive PCI (n=234) or no preventive PCI (n=231) in non-IRAs while they were still in the catheterization laboratory. The trial was stopped prematurely due to a highly significant difference in the primary outcome in favor of preventive PCI (p<0.001). The mean follow-up was 23 months. The primary composite outcome (a composite of death from cardiac causes, non-fatal myocardial infarction, or refractory angina) occurred in 21 patients in the preventive PCI group (9%) and 53 patients in the no preventive PCI group (22.9%), with a risk reduction of 65% in the preventive PCI group (hazard ratio-HR 0.35; 95% confidence intervals-CI, 0.21-0.58, p<0.001). This translates into an absolute risk reduction of 14% or a number needed to treat of 7 patients to prevent one primary endpoint event at 1 year. Cardiac death or non-fatal myocardial infarction occurred in 11 (4.7%) patients in the preventive PCI group and 27 (11.7%) patients in the no preventive PCI group (HR 0.36; 95% CI 0.18 – 0.73, p=0.004). This translates into an absolute risk reduction of 7% or a number needed to treat of 15 patients to prevent one cardiac death or nonfatal MI at 1 year. There was no difference between the two groups concerning procedure related complications, however the trial was not adequately powered for safety outcomes.

These robust results in favor of preventive acute-multi vessel PCI in STEMI are opposite to current standards of care and the PRAMI study is subject to criticism for several reasons.⁴⁵⁻⁴⁷ Patients were eligible if the culprit lesion had been treated successfully and there was ≥50% stenosis in one or more coronary arteries other than the IRA considered by the cardiologist as treatable by PCI. However, most studies define a stenosis as clinically significant if ≥70%, except for the left main artery. More recent guidelines define significant coronary disease as lesions >70% by angiography, or lesions that are hemodynamically significant by stress testing, FFR, or intravascular ultrasound.¹⁰ Furthermore, there was no core laboratory confirmation and the severity and location of the stenoses or the left ventricular ejection fraction were not

reported, which may lead to a misinterpretation of the results of the study. More patients who did not undergo preventive PCI had diabetes and anterior STEMI, which are important predictors of poor outcomes. As a result, it is possible that patients in the IRA-only PCI group were sicker than those in the preventive PCI group. Also patients who did not undergo preventive PCI would be more likely to report symptoms which would increase the recorded incidence of refractory angina and lead to more testing. By study design staged PCI in patients without angina was discouraged and further PCI should be performed only in cases of refractory angina and after objective assessment of ischemia. Thus acute multi-vessel PCI was not compared to a staged PCI strategy which is however the current mainstream approach for STEMI with MVD. The SWISSI II randomized trial found staged elective (non-acute) PCI to be superior to medical therapy for patients with proven silent myocardial ischemia after STEMI.⁴⁸ In a recent report by Dangas et al, staged PCI was the revascularization strategy in 80% of patients with STEMI and MVD, additional PCI in case of symptoms or ischemia in 14% of cases and acute multi-vessel PCI in only 2% of cases.¹³ Finally, in PRAMI study 2428 STEMI patients were screened but only 465 (about one out of five) were found eligible. Thus, the results of PRAMI study would be applicable to a minority of STEMI patients. Similar results should be replicated in other studies and the characteristics of STEMI patients that could benefit from acute preventive PCI should be precisely defined before considering preventive acute PCI for STEMI as a legitimate option.

WHAT TO DO WITH NON-CULPRIT LESIONS IN STEMI AND MVD?

The reduction in rates of cardiac death, myocardial infarction, or refractory angina by stenting of significant lesions in non IRAs could have two possible explanations. It can be obtained either by reducing ischemia from flow-limiting stenoses or by stabilizing unstable coronary lesions. The distinction is important because it would affect the optimal technique to identify the lesions that should be treated.

If benefit was confined to flow-limiting lesions, targeting of more severe stenoses or lesions selected by FFR may be preferred, with little gain from stenting less severe and non-flow-limiting stenoses. Complete revascularization using FFR testing to identify significant lesions has been shown to improve outcomes compared with revascularization based only on angiographic analysis.^{16,49} Flow-limiting lesions may be identified at the time of STEMI since FFR at time of primary PCI has been shown to correlate well with FFR obtained later when the patient is stabilized.⁵⁰ Thus, FFR can be considered

during the acute phase, but the results should be prudently used to support a decision for staged PCI.⁵⁰

On the other hand, if benefit is derived by treating lesions at risk because of instability, the measurement of FFR may have limited value, while consideration of angiographic appearances (e.g., lesion irregularity and ulceration), intravascular ultrasound and optical coherence tomography may better help target non-culprit lesions for stenting. In the prospective angiographic – intravascular ultrasound PROSPECT study involving patients undergoing PCI for acute coronary syndromes, most non-culprit lesions responsible for follow-up MACE were angiographically mild at baseline and more likely to be characterized by a plaque burden $\geq 70\%$, a minimal luminal area $\leq 4 \text{ mm}^2$ or to be classified on the basis of virtual histology as thin-cap fibroatheromas.¹⁸ However, non-culprit lesions with all three of the above characteristics were associated with MACE in only 18.2% of cases, which is an argument against stenting lesions that would be named “vulnerable” based on the above criteria.¹⁸ Thus, for the time being the evidence base for the selection of flow-limiting lesions by FFR is solid, which is not the case for “vulnerable” plaque detection by various intravascular imaging criteria (virtual histology, optical coherence tomography-OCT, near-infrared spectroscopy) where more research is needed.⁵¹

CONCLUSIONS

Current practice guidelines do not support acute multi-vessel PCI during non-shock STEMI. This concept is challenged by the recently published PRAMI study where preventive multi-vessel PCI in STEMI has been associated with reduction of MACE compared to the conservative approach of IRA-only PCI. Multi-vessel PCI may be necessary in some STEMI patients who have multiple critical lesions and do not improve after IRA-only PCI. This kind of patients probably could explain the results of the PRAMI trial, which however has limitations and has been subject to criticism. The results of ongoing randomized controlled trials are expected in order to clarify the optimal revascularization strategy after the IRA PCI for patients with STEMI and MVD.⁵²

MVD in STEMI is not a single entity and thus the treatment approach should be individualized.⁴ A decisional algorithm is proposed (Fig. 3). Primary PCI of the IRA still remains the default strategy in non-shock STEMI according to the guidelines and despite the PRAMI study results. Acute multi-vessel PCI could be justified in patients with multiple critical lesions. Significant lesions of the non-infarct arteries should be timely treated by staged PCI procedures that should be justified because of symptoms or positive functional tests.

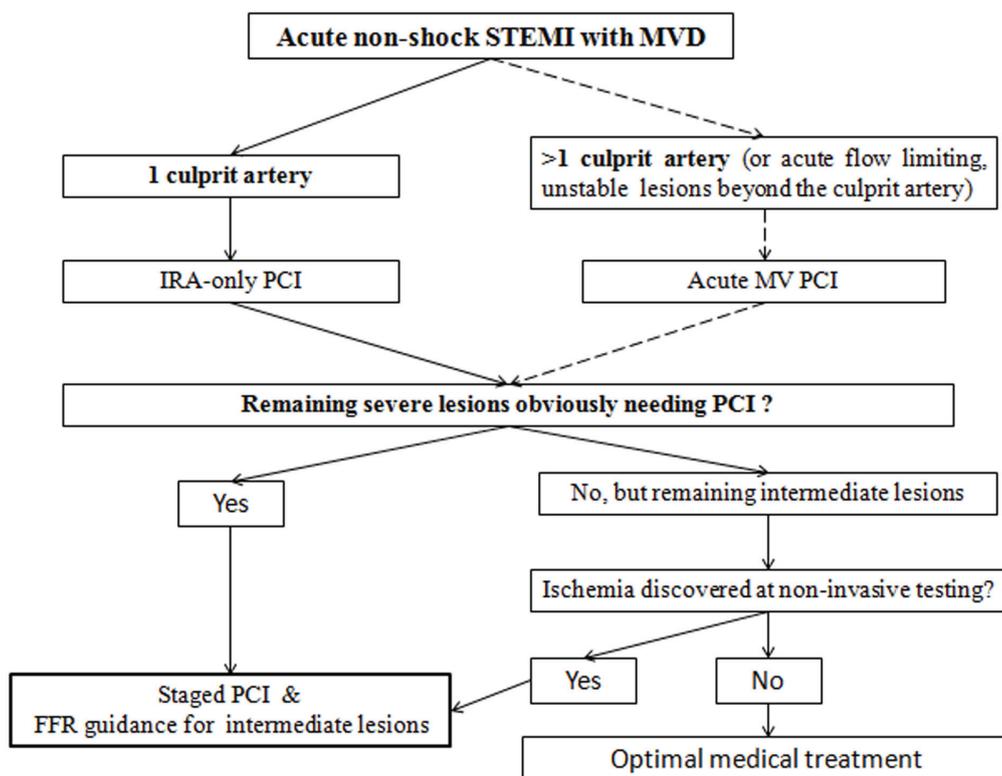


FIGURE 3. Suggested decisional algorithm for PCI revascularization in non-shock cases of acute STEMI with MVD. MVD = multi-vessel (coronary artery) disease; PCI = percutaneous coronary intervention; STEMI = ST-elevation myocardial infarction.

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