Review

Percutaneous coronary intervention strategies in patients with acute myocardial infarction and multivessel disease: Completeness, timing, lesion assessment, and patient status

Yuichi Saito (MD)[a,b,*], Yoshio Kobayashi (MD, FJCC)[a]

[a] Department of Cardiovascular Medicine, Chiba University Graduate School of Medicine, Chiba, Japan
[b] Yale University School of Medicine, New Haven, CT, USA

A B S T R A C T

Approximately 50% of patients with acute myocardial infarction including ST segment elevation myocardial infarction and non-ST segment elevation myocardial infarction have multivessel (MV) coronary artery disease. Recently, the evidence for beneficial outcomes associated with MV percutaneous coronary intervention (PCI) compared with culprit-only PCI has increased. However, optimal timing of non-culprit revascularization, appropriate lesion assessment in non-culprit vessels, and the best treatment strategy for patients with cardiogenic shock remain unclear. This review summarizes current evidence and focuses on the PCI strategies in patients with acute myocardial infarction and MV disease.

© 2019 Published by Elsevier Ltd on behalf of Japanese College of Cardiology.

Contents

Introduction

In a substantial proportion of patients with acute myocardial infarction (MI), atherosclerosis is not limited to a single lesion or vessel, but involves multiple vessels. Approximately 50% of patients with acute MI including ST segment elevation myocardial infarction (STEMI) and non-ST segment elevation myocardial infarction (NSTEMI) have multivessel (MV) coronary artery disease (CAD) [1,2]. The short-term prognosis after acute MI is worse with MV CAD than single-vessel CAD, probably due to additional plaque instability, impaired myocardial perfusion, or decreased contractility in non-infarct areas [3]. Patients with acute MI with MV CAD also have worse long-term outcomes compared to subjects with less extensive CAD [4]. Primary percutaneous coronary intervention (PCI) and early invasive strategy have been shown to contribute to a major improvement in prognosis for patients with acute MI [5]. However, the optimal revascularization strategy with PCI in patients with acute MI and MV CAD remains unclear. Treatment options and unresolved issues for these patients include

* Corresponding author at: Department of Cardiovascular Medicine, Chiba University Graduate School of Medicine, 1-8-1 Inohana, Chuo-ku, Chiba, Chiba 260-8677, Japan.
E-mail address: saitoyuichi1984@gmail.com (Y. Saito).

completeness and timing of PCI, assessment of ischemia, and patient status. This article provides an in-depth review of current evidence of PCI strategies in patients with acute MI and MV CAD.

Completeness of multivessel revascularization

The primary goal during the primary PCI procedure is to achieve revascularization of the culprit lesion, resolving patient's chest symptoms, and improving prognosis. Once the culprit lesion has been revascularized in patients with acute MI and MV CAD, complete revascularization should be considered. In the 2018 European Society of Cardiology (ESC) guideline on myocardial revascularization, the key massages include the need to achieve complete revascularization [6]. Regarding complete revascularization in patients with acute MI, observational data have shown widely varying results for the comparison of culprit-only versus MV PCI. Among 16 meta-analyses including observational data with STEMI and MV CAD, five (31%) showed increased mortality, six (38%) showed similar mortality, and five (31%) showed lower mortality associated with MV PCI compared to culprit-only PCI [7]. Given the selection biases and confounding factors that remained in the observational studies even after statistical adjustment, the results were not definitive enough to draw a conclusion. In fact, a previous study clearly showed that clinicians are more disposed to perform complete revascularization during primary PCI in higher risk patients, leading to the selection bias in the observational studies [8]. A randomized controlled trial (RCT) comparing revascularization strategies in patients with acute MI and MV CAD was first published in 2004 [9], followed by several small RCTs. The PRAMI trial, which had a considerably larger sample size than the previous studies, was published in 2013 (Table 1) [10]. This multicenter study enrolled a total of 465 STEMI patients with MV CAD, and the patients were randomly assigned either to no further PCI (n = 231) or to undergo immediate MV PCI in non-culprit vessels with ≥50% angiographic stenosis (n = 234), after completion of primary PCI in the culprit lesion. Recruitment

was prematurely halted due to a significant difference between the two groups. The composite primary outcome of cardiac death, non-fatal MI, or refractory angina occurred in 21 patients (9.0%) treated with MV primary PCI compared with 53 patients (22.9%) treated with culprit-only PCI [hazard ratio (HR) 0.35, 95% confidence interval (CI) 0.21–0.58, $p < 0.001$] [10]. In addition, there was a statistically significant reduction in the composite of cardiac death and non-fatal MI in MV primary PCI group. In this study, severe stenoses in the non-culprit vessels were left untreated in cases with the culprit-only primary PCI group (e.g. inferior STEMI with 90% angiographic stenosis in the proximal left anterior descending artery). Subsequently, the CvLPRIT trial included a total of 296 patients with STEMI and MV CAD [11]. Patients were randomly assigned to either culprit-only primary PCI (n = 146) or complete revascularization with MV PCI (n = 150) during the index procedure or as staged PCI. The composite primary outcome of all-cause death, MI, heart failure, and ischemia-driven revascularization at 12 months occurred in 15 patients (10.0%) with MV PCI compared to 31 patients (21.2%) with culprit-only PCI (HR 0.45, 95% CI 0.24–0.84, $p = 0.009$). There was no significant difference for the individual endpoints, although the trends favored MV PCI [11]. In the DANAMI-3-PRIMULTI trial, a total of 627 STEMI patients with angiographic stenosis >50% in non-culprit vessels were randomly assigned to either fractional flow reserve (FFR)-guided complete revascularization two days after the index PCI (n = 314) or no further invasive treatment (n = 313) [12]. Of note, 97 patients (31%) in the FFR-guided complete revascularization group did not undergo staged PCI owing to FFR values >0.80 in the non-culprit vessels. Patients allocated to complete revascularization had a lower major vascular cardiac events (MACE) rate (a composite of all-cause death, MI, or ischemia-driven revascularization in non-culprit vessel) than those assigned to culprit-only PCI (13.0% vs. 22.0%, $p = 0.004$), mainly driven by reduced repeat revascularization. There were no differences in mortality or MI rates [12]. The COMPARE-ACUTE trial, which is the latest and largest RCT as of early 2019 to investigate different treatment strategies in patients

Table 1
Key randomized controlled trials comparing revascularization strategies in patients with acute MI and MV CAD.

Study/first author Year	Patient status	Sample size	Tested strategies	Assessment of non-culprit lesions	MACE/MACCE rate
Politi et al. [21] 2010	STEMI	214	CVO PCI vs. MV primary PCI vs. MV staged PCI	%DS ≥70%	50.0% vs. 23.1% vs. 20.0% ($p < 0.001$)[a] at 2.5 years
PRAMI [10] 2013	STEMI	465	CVO PCI vs. MV primary PCI	%DS ≥50%	22.9% vs. 9.0% ($p < 0.001$)[b] at 23 months
CvLPRIT [11] 2015	STEMI	296	CVO PCI vs. MV primary or staged PCI	%DS >70% in 1 view or >50% in 2 views	21.2% vs. 10.0% ($p = 0.009$)[c] at 12 months
DANAMI-3-PRIMULTI [12] 2015	STEMI	627	CVO PCI vs. MV staged PCI	%DS >50% with FFR ≤0.80	22.0% vs. 13.0% ($p = 0.004$)[d] at 27 months
SMILE [22] 2016	NSTEMI	542	Immediate MV PCI vs. MV staged PCI	Not reported	13.6% vs. 23.2% ($p = 0.004$)[e] at 1 year
COMPARE-ACUTE [13] 2017	STEMI	885	CVO PCI vs. MV primary or staged PCI	%DS ≥50% with FFR ≤0.80	20.5% vs. 7.8% ($p < 0.001$)[f] at 1 year
CULPRIT-SHOCK [33] 2017	Acute MI with cardiogenic shock	686	CVO PCI vs. MV primary PCI	%DS >70%	45.9% vs. 55.4% ($p = 0.01$)[g] at 30 days

%DS, angiographic percentage of diameter stenosis; ACS, acute coronary syndrome; CAD, coronary artery disease; CVO, culprit vessel-only; FFR, fractional flow reserve; MACCE, major adverse cardiovascular and cerebrovascular events; MACE, major adverse cardiac events; MI, myocardial infarction; MV, multivessel; NSTEMI, non-ST segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST segment elevation myocardial infarction; TVR, target vessel revascularization.

[a] MACE was a composite of death, MI, rehospitalization for ACS, and any repeat revascularization.
[b] MACE was a composite of cardiovascular death, non-fatal MI, refractory angina.
[c] MACE was a composite of death, MI, any repeat revascularization, and heart failure.
[d] MACE was a composite of death, MI, and any repeat revascularization of non-culprit vessel.
[e] MACCE was a composite of cardiac death, MI, rehospitalization for unstable angina, TVR, and stroke.
[f] MACCE was a composite of death, MI, any repeat revascularization, and cerebrovascular events.
[g] MACE was a composite of death and renal-replacement therapy.

with STEMI and MV CAD (angiographic stenosis ≥50%), enrolled a total of 885 subjects [13]. Following primary PCI of the culprit vessel, patients were randomly assigned in a 1:2 ratio to either complete revascularization of non-culprit vessels under FFR guidance (n = 295) or to FFR assessment with no further treatment (n = 590). In the culprit-only PCI group, both the patients and physicians were unaware of the FFR findings. FFR assessment led to 46% of the patients in the complete revascularization group receiving no further treatment owing to discriminating FFR values >0.80 in the non-culprit vessels. Among the patients who received PCI of non-culprit lesions, 83% underwent MV primary PCI, whereas staged PCI was performed in the rest of 17%. At 1 year, complete revascularization under FFR guidance group had a significantly lower rate of the composite endpoint (death, MI, revascularization, and cerebrovascular events) compared to the culprit-only PCI group (7.8% vs. 20.5%, p < 0.001). The difference between the two groups was mainly driven by revascularization, although clinically indicated elective PCI within 45 days of the primary procedure was not counted as an event in the culprit vessel-only PCI group in this study, and was performed in 10% of patients in that group. Notably, the patients with untreated lesions with an FFR ≤0.80 in non-culprit vessel had a higher rate of the composite endpoint than those with treated (30.7% vs. 8.9%, p < 0.001) [13]. These four RCTs, PRAMI, CvLPRIT, DANAMI-3-PRIMULTI, and COMPARE-ACUTE, have consistently shown the safety and benefit of complete revascularization compared with culprit-only PCI in patients with STEMI and MV CAD (Table 1), but also had several limitations. The included patients had relatively low-risk features according to the inclusion criteria, and were only eligible for enrolment into the trial if the physician considered the non-culprit lesion(s) suitable for PCI. Furthermore, sample sizes and therefore statistical power to detect differences in hard events (i.e. death or MI) were limited in these RCTs. Although a recent meta-analysis (n = 3561) which included 11 RCTs comparing complete revascularization with culprit-only PCI in patients with STEMI and MV CAD without cardiogenic shock indicated that complete revascularization significantly reduced a risk for death and MI [relative risk (RR) 0.76, 95% CI, 0.58–0.99, p = 0.04] [14], further studies are warranted. In addition, whether the results of the RCTs with STEMI patients can be extrapolated to NSTEMI is unclear. Since no large-scale RCTs have addressed the issue, the benefits of complete revascularization in NSTEMI patients with MV CAD remains unknown. Several observational studies, however, demonstrated benefits of complete revascularization in patients with NSTEMI. In the ACUITY trial, which enrolled 2954 patients with non-ST segment elevation acute coronary syndrome (ACS), incomplete revascularization was associated with an increased risk of MACE [15]. A recent large-scale cohort study with 21,857 NSTEMI patients with MV CAD also indicated that complete revascularization strategy appeared to be superior to culprit-only PCI in terms of long-term mortality (HR 0.90, 95% CI 0.85–0.97) [2]. Therefore, complete revascularization should be considered in patients with acute MI and MV CAD, especially in STEMI. The 2017 ESC guidelines support complete revascularization strategy as Class IIa recommendation [16], whereas the US guidelines in 2015 allow it with Class IIb indication [17].

Complete revascularization during index procedure vs. staged multivessel PCI

Most of the studies support the concept of complete revascularization in patients with acute MI, but there is a lack of evidence on the optimal timing of MV revascularization. PCI of non-culprit lesion should be performed either immediately during the primary procedure or as a staged treatment, unless the patient is indicated for complete revascularization by coronary artery bypass grafting based on the Heart Team decision, depending on clinical characteristics, and anatomical and technical aspects [6]. The potential advantages of immediate MV primary PCI include prevention of recurrent ischemia and infarction, and improvement in myocardial function in the early phase after acute MI. Lower risk for bleeding and vascular complications with favorable effect on healthcare costs may be additional benefits [18]. A pre-specified subgroup analysis of the CvLPRIT trial showed that infarct size following complete revascularization in STEMI patients which was assessed by cardiac magnetic resonance imaging (CMR) was significantly smaller in MV primary PCI group (n = 63) compared to staged MV PCI group (n = 30) (11.6% vs. 19.7% of left ventricular mass, p = 0.01) [19]. On the other hand, immediate MV PCI strategy may carry potential harm with concerns for poor assessment of lesion severity in non-culprit vessel, prothrombotic and inflammatory milieu by additional stenting, prolonged procedure time in the catheter laboratory, and acute kidney injury due to increased contrast volume [18]. In fact, MV PCI during index procedure was reportedly associated with higher complication rate [18]. Potential risks and benefits of the two strategies are summarized in Fig. 1.

There have been only three small RCTs in the setting of STEMI and one RCT in NSTEMI that directly evaluated immediate versus staged MV PCI [20]. Politi et al. reported a RCT that enrolled 214 patients with STEMI and MV CAD, comparing the three strategies, culprit-only PCI (n = 84), MV primary PCI (n = 65), and staged MV PCI (n = 65) (Table 1) [21]. During a mean follow-up of 2.5 years, 42 patients (50.0%) in the culprit-only PCI group experienced at least one MACE, a composite of death, ACS, and any repeat revascularization, 13 (20.0%) in the MV primary PCI group, and 15 (23.1%) in the staged MV PCI group (p < 0.001), with no differences in death or MI rates. There were some limitations in this RCT, such as being single-center study, the small-sample size, and low rate of drug-eluting stent (DES) use (9.6%) [21]. Among patients with NSTEMI, the SMILE trial enrolled a total of 542 patients with MV CAD who were scheduled to undergo an early invasive strategy (PCI within 24 h), and compared immediate MV PCI during index procedure with PCI of only the culprit vessel, followed by staged procedure (Table 1) [22]. The PCI procedures in this study have been performed in contemporary settings with radial access rate of 84% and DES use of 85%, and 26% of patients underwent FFR measurement. The incidence of the primary endpoint, a composite of cardiac death, MI, rehospitalization for unstable angina, repeat revascularization, and stroke, was significantly lower in the immediate MV PCI group than the counterpart (13.6% vs. 23.2%, p = 0.004). Although the difference was mainly driven by reduced repeat revascularization (8.3% vs. 15.2%, p = 0.01), the incidence of all-cause death presented a trend in favor of immediate MV PCI group (6.4% vs. 11.0%, p = 0.06). Understandably, procedure time [61 (38–79) min vs. 44 (28–59) min, p < 0.001] and contrast volume [295 (195–400) ml vs. 180 (140–230) ml, p < 0.001] during the index procedure were greater in the immediate MV PCI group. The authors concluded that immediate MV PCI was superior to multistage PCI in patients with NSTEMI and MV CAD [22]. However, several weaknesses of this study were pointed out in the editorial comment as follows: (1) the incidence of repeat revascularization in the multistage PCI group was unprecedentedly high in the DES era (15.4% at 1 year). (2) The event rates unexpectedly start to diverge after 6 months. (3) Patients with an estimated glomerular filtration rate <60 ml/min/m² were excluded from the study [23]. A meta-analysis (n = 838) that analyzed four RCTs including the report by Politi et al. and the SMILE trial showed the safety and effectiveness of immediate MV PCI compared with multistage PCI in patients with acute MI, largely driven by the SMILE trial [20]. Given the limitations of these RCTs, it is difficult to directly assess the optimal timing of MV revascularization.
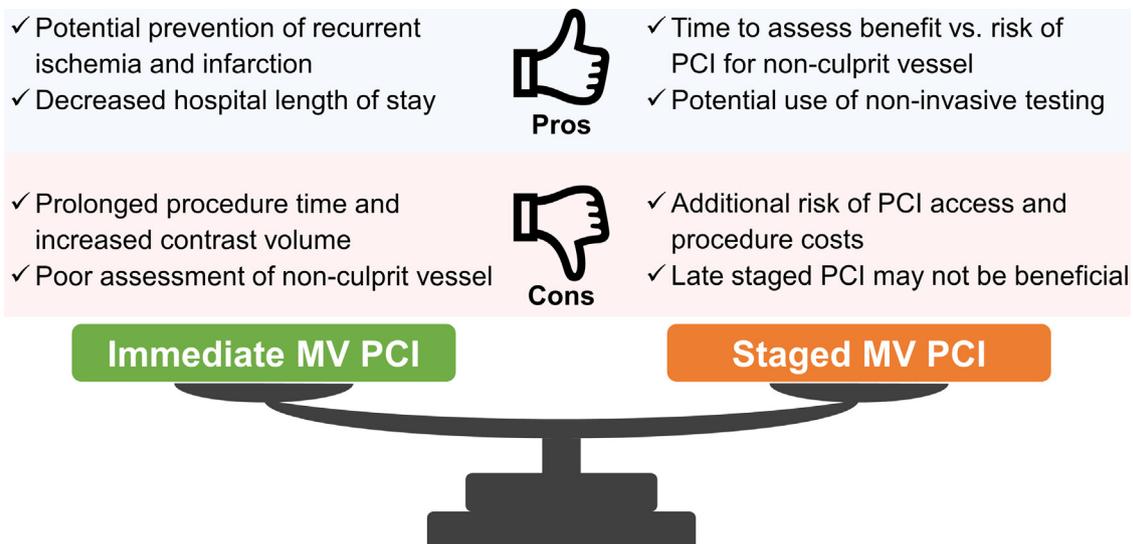
Fig. 1. Potential risks and benefits of immediate MV PCI during index procedure vs. staged MV PCI. MV, multivessel; PCI, percutaneous coronary intervention.

In the observational studies, immediate MV PCI during index procedure has been consistently shown to be associated with worse clinical outcomes than staged MV PCI. A meta-analysis of seven observational studies in patients with STEMI ($n = 2653$) indicated higher mortality in immediate MV PCI group without heterogeneity [odds ratio (OR) 3.89, 95% CI 2.65–5.70, I-squared 0%] [3]. As mentioned above, a more critical clinical condition may have biased the selection of patients for MV primary PCI. On the other hand, a recent meta-analysis that included 11 RCTs which did not necessarily compare the two strategies (i.e. MV primary PCI vs. staged MV PCI) directly, demonstrated that MV primary PCI was related to significant reduction in mortality and MI, whereas staged revascularization did not improve these outcomes compared with culprit-only PCI in patients with STEMI [14]. Interestingly, earlier complete revascularization (i.e. MV primary PCI or 'early' staged PCI) was associated with reduced risk for death or MI ($p = 0.03$). The study suggested that early staged revascularization within five days may lead to a significant benefit [14], possibly explained by higher event rate in STEMI within the first few days [1].

Feasibility of immediate complete revascularization during index procedure largely depends on the clinical settings such as patient and lesion characteristics (Table 2) [24]. Although evidence is rather scarce, a strategy of complete revascularization during index procedure should be considered in patients with acute MI and MV CAD, when feasible and applicable. The 2017 ESC guidelines recommend complete revascularization before discharge (Class IIa), but do not support either an immediate or a staged strategy [16]. Early staged MV PCI may also be beneficial.

Non-culprit vessel assessment by angiography, FFR, or non-invasive testing

Complete revascularization in patients with acute MI and MV CAD has been investigated in numerous observational studies, RCTs, and meta-analyses, especially in STEMI patients. However, the definition of complete revascularization varies among the studies, based on angiographic percentage of diameter stenosis (%DS), SYNTAX score, or physiological assessment [25]. Although angiographic %DS has been most frequently used for assessment of complete revascularization, a post hoc analysis of the ACUITY trial ($n = 2954$) demonstrated that with the use of %DS cut-off values ≥30%, ≥40%, ≥50%, ≥60%, and ≥70% for defining 'significant' CAD, the prevalence of achieved complete revascularization after PCI in patients with non-ST segment elevation ACS was 25%, 45%, 63%, 75%, and 83%, respectively [15]. The result indicated that 'complete revascularization' depends on the definitions. Recently, FFR-guided complete revascularization in patients with acute MI and MV CAD has been also investigated in large-scale RCTs [12,13]. The presence of local myocardial damage in the culprit vessel territory of acute MI patients could affect physiologic indices such as FFR and instantaneous wave-free ratio (iFR), but a previous report indicated that FFR values of the non-culprit stenoses in patients with acute MI did not change between the acute and follow-up (35 ± 4 days later) phase [26]. Although a large meta-analysis which included patients with stable CAD and non-ST segment elevation ACS ($n = 156,240$) showed that complete revascularization is associated with reduced risk of mortality and MACE, irrespective of the definitions such as angiographic %DS, SYNTAX

Table 2
Factors affecting timing of non-culprit PCI.

Factors favoring MV PCI during the index procedure	Factors favoring staged MV PCI
Ongoing chest pain/arrythmias	Stable symptoms
Potentially unstable non-culprit lesion with large area of myocardium at risk	Chronic kidney disease
Infarct artery required little time and contrast	Prolonged procedure to open the culprit lesion
Anticipated simple PCI of non-infarct vessel	Complex lesion in non-infarct vessel
Patient and catheterization laboratory preference	Patient and catheterization laboratory preference

MV, multivessel; PCI, percutaneous coronary intervention.

score, and physiological assessment [25], it remains to be determined how clinicians can identify the lesions that should be revascularized beyond the culprit lesion in patients with acute MI and MV CAD.

Among 11 RCTs which were included in a meta-analysis, 8 trials used only angiography to define the significance of non-culprit lesions, whereas 3 trials also used a functional assessment of non-culprit lesions with FFR in STEMI patients with MV CAD [14]. RCTs using angiography had a significant risk reduction in risk for death or MI (RR 0.70, 95% CI 0.52–0.96, p = 0.03), meanwhile trials using FFR had a non-significant trend for risk reduction (RR: 0.90, 95% CI 0.47–1.70, p = 0.70) [14]. Of note, in the DANAMI-3-PRIMULTI and COMPARE-ACUTE trial, FFR-guided MV PCI resulted in 31% and 46% of patients receiving no further PCI after primary procedure despite significant non-culprit lesions on angiographical assessment, with reduced risks of MACE [12,13]. A post hoc study combining the data from three RCTs showed that incomplete revascularization defined by residual SYNTAX score was not associated with MACE in patients with ACS in the setting of complete functional revascularization under FFR guidance, indicating that functional complete revascularization is an applicable method and more important goal even in ACS patients [27]. Furthermore, although a strategy with non-invasive stress testing after index PCI, followed by staged PCI if indicated, is another option for patients with acute MI and MV CAD, few studies have examined it [7]. The 2017 ESC guidelines for STEMI allowed non-invasive stress testing during hospital stay after primary PCI to assess myocardial ischemia and viability as Class IIb indication with level of evidence C [16]. The 2016 appropriate use criteria for coronary revascularization in patients with ACS indicated that immediate PCI of non-culprit vessel (≥50% stenosis) during index procedure following PCI of culprit vessel 'may be appropriate' in hemodynamically stable STEMI patients, whereas staged PCI of non-culprit vessel with evidence of ischemia assessed by FFR or non-invasive testing during the initial hospitalization in asymptomatic patients is rated as 'appropriate' [28]. Additionally, a Japanese consensus document for acute MI recommends using physiological assessments including FFR, iFR, and quantitative flow ratio before staged PCI in non-culprit vessel [29]. The results of these studies and guideline recommendations may suggest that indications of revascularization for non-culprit lesion should match elective PCI standards, and complete revascularization should be achieved if indicated [3,29].

STEMI vs. NSTEMI

A body of evidence has accumulated regarding PCI strategies in patients with STEMI and MV CAD, whereas data are sparse in NSTEMI patients, as described above. The SMILE trial is the only large-scale RCT as of early 2019, which tested the PCI strategy in patients with NSTEMI and MV CAD, but did not have a culprit-only PCI arm (Table 1) [22]. An important difference between STEMI and NSTEMI is the difficulty of determining the culprit lesion. It tends to be obvious in STEMI, but in NSTEMI is not always possible. Approximately 40% of patients with NSTEMI and MV CAD reportedly have at least two lesions with angiographic findings as culprit lesion [2], possibly leading to few studies investigating PCI strategies in NSTEMI patients with MV CAD. Thus, intracoronary imaging to identify the culprit lesion and invasive physiological indices to assess the lesion severity can play important roles in this population. In addition, the current recommendations on the timing of angiography and intervention in patients with NSTEMI are based on risk stratification, and coronary artery bypass grafting should be considered in the stabilized subject with complex cases, whereas primary PCI without any time delay is indicated in STEMI patients [5,6]. Fur-

thermore, pharmacological action may be different between STEMI and NSTEMI [30]. Although guideline recommendations are in the same direction between STEMI and NSTEMI with MV CAD [6], the evidence for NSTEMI patients with MV CAD are largely based on observational studies and extrapolation of the results of STEMI trials. Therefore, careful interpretation and further investigations are required, especially in patients with NSTEMI and MV CAD.

Cardiogenic shock

Among patients with acute MI, 5–10% of patients present with cardiogenic shock and have high in-hospital mortality at 40–50% despite the increasing use of primary PCI [31]. Although supporting evidence had been scarce, guidelines (e.g. 2017 ESC guidelines for STEMI) had recommended MV primary PCI during index procedure as Class IIa mainly based on expert consensus and pathophysiological considerations in STEMI patients with MV CAD and cardiogenic shock [16]. Complete revascularization with preemptive interventions on non-culprit vessels during index procedure has been thought to be beneficial in improving ventricular function and hemodynamic status. However, observational studies have not necessarily shown an advantage of MV primary PCI [32]. Against this background, 30-day and 1-year results of the CULPRIT-SHOCK trial, which enrolled 685 acute MI (i.e. both STEMI and NSTEMI) patients with MV CAD and cardiogenic shock, were reported [33,34]. Patients were randomly allocated into an angiography-guided immediate MV PCI (including intervention of chronic total occlusion) or culprit-only PCI with possible staged revascularization in the study (Table 1). The primary endpoint was a composite of death or renal-replacement therapy within 30 days after randomization. At 30 days, immediate MV PCI group showed significantly higher risk of primary endpoint (55.4% vs. 45.9%, p = 0.01) as well as all-cause death alone (51.6% vs. 43.3%, p = 0.03) compared with culprit-only PCI group [33]. At 1-year follow-up, all-cause death still tended to be higher in the immediate MV PCI group, with no mortality difference between 30 days and 1 year. On the other hand, the rates of rehospitalization for heart failure and repeat revascularization were lower in the immediate MV PCI than culprit-only PCI group [34]. According to this result, the 2018 ESC guideline was updated to indicate routine revascularization of non-culprit vessels in MI with cardiogenic shock during primary PCI as Class III [6]. The CULPRIT-SHOCK trial provided compelling data in this extremely high-risk population, but a judicious interpretation is warranted. In this study, more than 50% of the patients underwent resuscitation before PCI, and increased risk of death in the immediate MV PCI group was mostly due to brain injury. Moreover, chronic total occlusions were present in 24% of the patients in the immediate MV PCI group, and complete revascularization could not be achieved in 19% [33]. Revascularization of CTO in the non-culprit vessel during index procedure would likely not be routinely intervened in clinical settings. Thus, whether anticipated simple PCI of non-culprit vessel during index procedure is beneficial or harmful is still unclear especially in non-resuscitated patients. However, routine immediate MV PCI should be avoided in acute MI with cardiogenic shock. An algorithm of PCI strategies in patients with acute MI and MV CAD is shown in Fig. 2.

Upcoming trials

To improve the current limited knowledge, several large-scale RCTs are ongoing (Table 3). The COMPLETE trial, which compares FFR-guided staged MV PCI with culprit-only PCI as well as the DANAMI-3-PRIMULTI trial, will be the first RCT with the statistical power to detect differences in the incidence of death or MI between treatment strategies in patients with STEMI. This study
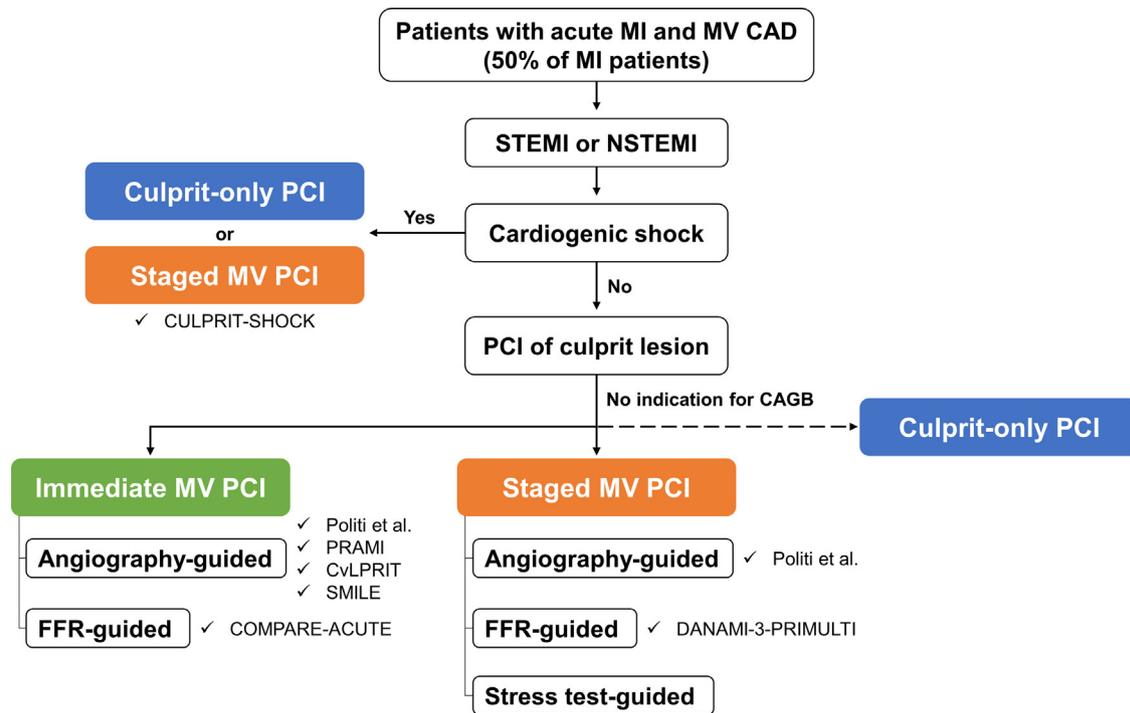
Fig. 2. Decision process and revascularization options in patients with acute MI and MV CAD. Approximately 50% of patients with acute MI including STEMI and NSTEMI have MV CAD. Although guideline recommendations are in the same direction between STEMI and NSTEMI with MV CAD, data are sparse in NSTEMI patients. In patients with cardiogenic shock, routine immediate MV PCI during index procedure should be avoided. In patients without cardiogenic shock and indication for CABG, immediate or staged MV PCI should be considered if indicated. Supporting evidence of randomized controlled trials are listed. CABG, coronary artery bypass grafting; CAD, coronary artery disease; FFR, fractional flow reserve; MI, myocardial infarction; MV, multivessel; NSTEMI, non-ST segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST segment elevation myocardial infarction.

Table 3
Ongoing large-scale RCTs in patients with acute MI and MV CAD.

	COMPLETE	FULL REVASC	FRAME-AMI	iMODERN
Clinical trial number	NCT01740479	NCT02862119	NCT02715518	NCT03298659
Sample size	4042	4052	1292	1146
Estimated completion	October 2018	June 2021	June 2020	January 2021
Type of MI	STEMI	STEMI and NSTEMI	STEMI and NSTEMI	STEMI
Assessment of non-culprit lesions	%DS ≥70% or %DS ≥50% with FFR ≤0.80	%DS ≥50% with FFR ≤0.80 (FFR is not mandatory for lesions with %DS 90–99%)	%DS ≥50% with FFR ≤0.80 (FFR is not mandatory for lesions with %DS >90%) or %DS ≥50%	%DS ≥50% with iFR ≤0.89 or %DS ≥50% with ischemic evidence by stress perfusion CMR
Design	Staged MV PCI (<72 h) vs. CVO primary PCI	MV PCI during index procedure or hospitalization vs. CVO primary PCI	FFR-guided vs. angiography-guided MV PCI	iFR-guided immediate MV PCI vs. stress CMR-guided staged MV PCI
Primary endpoint	4-year CV death and MI (plus IDR)	1-year death and MI	2-year death and MI	1-year death, MI, and rehospitalization for HF

%DS, angiographic percentage of diameter stenosis; CAD, coronary artery disease; CMR, cardiac magnetic resonance imaging; CV, cardiovascular; CVO, culprit vessel-only; FFR, fractional flow reserve; HF, heart failure; IDR, ischemia-driven revascularization; iFR, instantaneous wave-free ratio; MI, myocardial infarction; MV, multivessel; NSTEMI, non-ST segment elevation myocardial infarction; PCI, percutaneous coronary intervention; RCT, randomized controlled trial; STEMI, ST segment elevation myocardial infarction.

may also focus the spotlight on the staged PCI. The FULL REVASC trial is another large RCT that can directly assess hard endpoints. The results of these trials will influence future guidelines on the optimal PCI strategies in patients with acute MI and MV CAD. The FRAME-AMI trial tests the method of non-culprit lesion assessment, FFR- versus angiography-guided PCI, in patients with both STEMI and NSTEMI. The iMODERN trial compares iFR-guided immediate MV PCI with non-invasive stress test-guided staged MV PCI using CMR. This study can address the usefulness of iFR in non-culprit vessel, immediate intervention versus staged PCI, and non-invasive stress test-guided strategy. The FRAME-AMI and iMODERN trial will show the new perspectives in this field. In addition, there are also several upcoming RCTs such as the COCUA

(NCT01180218), CROSS-AMI (NCT01179126), and ASSIST-CMR (NCT01818960) trials. These studies focus on the MV primary PCI in STEMI patients, stress echocardiography-guided staged MV PCI, and impact of immediate MV PCI on infarct size assessed by CMR. These studies will fill the gap of current evidence in PCI strategies in patients with acute MI and MV CAD.

Conclusions

Complete revascularization in patients with acute MI and MV CAD should be considered during index PCI or at staged procedure when feasible and applicable. Optimal timing of non-culprit revascularization, appropriate lesion assessment in non-culprit

vessels, and the best treatment strategy for patients with cardiogenic shock remain uncertain. Future studies with statistical power are still warranted.

Funding

Conflicts of interest

References

[1] Park DW, Clare RM, Schulte PJ, Pieper KS, Shaw LK, Califf RM, et al. Extent, location, and clinical significance of non-infarct-related coronary artery disease among patients with ST-elevation myocardial infarction. JAMA 2014;312:2019–27.

[2] Rathod KS, Koganti S, Jain AK, Astroulakis Z, Lim P, Rakhit R, et al. Complete versus culprit-only lesion intervention in patients with acute coronary syndromes. J Am Coll Cardiol 2018;72:1989–99.

[3] Bates ER, Tamis-Holland JE, Bittl JA, O'Gara PT, Levine GN. PCI strategies in patients with ST-segment elevation myocardial infarction and multivessel coronary artery disease. J Am Coll Cardiol 2016;68:1066–81.

[4] Sorajja P, Gersh BJ, Cox DA, McLaughlin MG, Zimetbaum P, Costantini C, et al. Impact of multivessel disease on reperfusion success and clinical outcomes in patients undergoing primary percutaneous coronary intervention for acute myocardial infarction. Eur Heart J 2007;28:1709–16.

[5] Ozaki Y, Katagiri Y, Onuma Y, Amano T, Muramatsu T, Kozuma K, et al. CVIT expert consensus document on primary percutaneous coronary intervention (PCI) for acute myocardial infarction (AMI) in 2018. Cardiovasc Interv Ther 2018;33:178–203.

[6] Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J 2019;40:87–165.

[7] Vogel B, Mehta SR, Mehran R. Reperfusion strategies in acute myocardial infarction and multivessel disease. Nat Rev Cardiol 2017;14:665–78.

[8] Ahmad Y, Cook C, Shun-Shin M, Balu A, Keene D, Nijjer S, et al. Resolving the paradox of randomised controlled trials and observational studies comparing multi-vessel angioplasty and culprit only angioplasty at the time of STEMI. Int J Cardiol 2016;222:1–8.

[9] Di Mario C, Mara S, Flavio A, Imad S, Antonio M, Anna P, et al. Single vs. multivessel treatment during primary angioplasty: results of the multicentre randomised HEpacoat for cuLPrit or multivessel stenting for Acute Myocardial Infarction (HELP AMI) Study. Int J Cardiovasc Intervent 2004;6:128–33.

[10] Wald DS, Morris JK, Wald NJ, Chase AJ, Edwards RJ, Hughes LO, et al. Randomized trial of preventive angioplasty in myocardial infarction. N Engl J Med 2013;369:1115–23.

[11] Gershlick AH, Khan JN, Kelly DJ, Greenwood JP, Sasikaran T, Curzen N, et al. Randomized trial of complete versus lesion-only revascularization in patients undergoing primary percutaneous coronary intervention for STEMI and multivessel disease: the CvLPRIT trial. J Am Coll Cardiol 2015;65:963–72.

[12] Engstrøm T, Kelbæk H, Helqvist S, Høfsten DE, Kløvgaard L, Holmvang L, et al. Complete revascularisation versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease (DANAMI-3–PRIMULTI): an open-label, randomised controlled trial. Lancet 2015;386:665–71.

[13] Smits PC, Abdel-Wahab M, Neumann FJ, Boxma-de Klerk BM, Lunde K, Schotborgh CE, et al. Fractional flow reserve-guided multivessel angioplasty in myocardial infarction. N Engl J Med 2017;376:1234–44.

[14] Pasceri V, Patti G, Pelliccia F, Gaudio C, Speciale G, Mehran R, et al. Complete revascularization during primary percutaneous coronary intervention reduces death and myocardial infarction in patients with multivessel disease: meta-analysis and meta-regression of randomized trials. JACC Cardiovasc Interv 2018;11:833–43.

[15] Rosner GF, Kirtane AJ, Genereux P, Lansky AJ, Cristea E, Gersh BJ, et al. Impact of the presence and extent of incomplete angiographic revascularization after percutaneous coronary intervention in acute coronary syndromes: the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial. Circulation 2012;125:2613–20.

[16] Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2018;39:119–77.

[17] Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, et al. 2015 ACC/AHA/SCAI focused update on primary percutaneous coronary intervention for patients with ST-elevation myocardial infarction: an update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention and the 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction. J Am Coll Cardiol 2016;67:1235–50.

[18] Bagai A, Thavendiranathan P, Sharieff W, Al Lawati HA, Cheema AN. Non-infarct-related artery revascularization during primary percutaneous coronary intervention for ST-segment elevation myocardial infarction: a systematic review and meta-analysis. Am Heart J 2013;166:684–93.

[19] Khan JN, Nazir SA, Greenwood JP, Dalby M, Curzen N, Hetherington S, et al. Infarct size following complete revascularization in patients presenting with STEMI: a comparison of immediate and staged in-hospital non-infarct related artery PCI subgroups in the CvLPRIT study. J Cardiovasc Magn Reson 2016;18:85.

[20] Gaffar R, Habib B, Filion KB, Reynier P, Eisenberg MJ. Optimal timing of complete revascularization in acute coronary syndrome: a systematic review and meta-analysis. J Am Heart Assoc 2017;6:e005381.

[21] Politi L, Sgura F, Rossi R, Monopoli D, Guerri E, Leuzzi C, et al. A randomised trial of target-vessel versus multi-vessel revascularisation in ST-elevation myocardial infarction: major adverse cardiac events during long-term follow-up. Heart 2010;96:662–7.

[22] Sardella G, Lucisano L, Garbo R, Pennacchi M, Cavallo E, Stio RE, et al. Single-staged compared with multi-staged PCI in multivessel NSTEMI patients: the SMILE trial. J Am Coll Cardiol 2016;67:264–72.

[23] Henriques JP, Claessen BE. A SMILE and a Frown: one-stage or multistage PCI in NSTEMI patients with multivessel disease. J Am Coll Cardiol 2016;67:273–4.

[24] Dangas GD, George JC, Weintraub W, Popma JJ. Timing of staged percutaneous coronary intervention in multivessel coronary artery disease. JACC Cardiovasc Interv 2010;3:1096–9.

[25] Nagaraja V, Ooi SY, Nolan J, Large A, De Belder M, Ludman P, et al. Impact of incomplete percutaneous revascularization in patients with multivessel coronary artery disease: a systematic review and meta-analysis. J Am Heart Assoc 2016;5:e004598.

[26] Ntalianis A, Sels JW, Davidavicius G, Tanaka N, Muller O, Trana C, et al. Fractional flow reserve for the assessment of nonculprit coronary artery stenoses in patients with acute myocardial infarction. JACC Cardiovasc Interv 2010;3:1274–81.

[27] Kobayashi Y, Lonborg J, Jong A, Nishi T, De Bruyne B, Hofsten DE, et al. Prognostic value of the residual SYNTAX score after functionally complete revascularization in ACS. J Am Coll Cardiol 2018;72:1321–9.

[28] Patel MR, Calhoon JH, Dehmer GJ, Grantham JA, Maddox TM, Maron DJ, et al. ACC/AATS/AHA/ASE/ASNC/SCAI/SCCT/STS 2016 appropriate use criteria for coronary revascularization in patients with acute coronary syndromes: a report of the American College of Cardiology Appropriate Use Criteria Task Force, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and the Society of Thoracic Surgeons. J Am Coll Cardiol 2017;69:570–91.

[29] Kawase Y, Matsuo H, Akasaka T, Shiono Y, Tanaka N, Amano T, et al. Clinical use of physiological lesion assessment using pressure guidewires: an expert consensus document of the Japanese Association of Cardiovascular Intervention and Therapeutics. Cardiovasc Interv Ther 2019;34:85–96.

[30] Wakabayashi S, Kitahara H, Nishi T, Sugimoto K, Nakayama T, Fujimoto Y, et al. Platelet inhibition after loading dose of prasugrel in patients with ST-elevation and non-ST-elevation acute coronary syndrome. Cardiovasc Interv Ther 2018;33:239–46.

[31] Kolte D, Khera S, Aronow WS, Mujib M, Palaniswamy C, Sule S, et al. Trends in incidence, management, and outcomes of cardiogenic shock complicating ST-elevation myocardial infarction in the United States. J Am Heart Assoc 2014;3:e000590.

[32] de Waha S, Jobs A, Eitel I, Poss J, Stiermaier T, Meyer-Saraei R, et al. Multivessel versus culprit lesion only percutaneous coronary intervention in cardiogenic shock complicating acute myocardial infarction: a systematic review and meta-analysis. Eur Heart J Acute Cardiovasc Care 2018;7:28–37.

[33] Thiele H, Akin I, Sandri M, Fuernau G, de Waha S, Meyer-Saraei R, et al. PCI strategies in patients with acute myocardial infarction and cardiogenic shock. N Engl J Med 2017;377:2419–32.

[34] Thiele H, Akin I, Sandri M, de Waha-Thiele S, Meyer-Saraei R, Fuernau G, et al. One-year outcomes after PCI strategies in cardiogenic shock. N Engl J Med 2018;379:1699–710.