

Current Status of Coronary Intervention in Patients with ST-Segment Elevation Myocardial Infarction and Multivessel Coronary Artery Disease

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Primary percutaneous coronary intervention (PCI) is a standard interventional treatment modality for ST-segment elevation myocardial infarction (STEMI). Diagnostic coronary angiogram during PCI reveals multivessel coronary artery disease in about half of patients with STEMI, and it is difficult to make decision on the extent of intervention in these patients. Although revascularization for the infarct-related artery only is still effective for STEMI patients, several studies have reported the efficacy of multivessel revascularization during primary PCI, as well as in a staged PCI procedure. Clinicians should consider clinical aspects such as initial cardiogenic shock and myocardial viability when performing primary multivessel intervention, including the risks and benefits of multivessel revascularization in patients undergoing primary PCI. This review describes the current status of performing multivessel PCI in patients with STEMI and proposes an optimal revascularization strategy based on the previous literature. (**Korean Circ J 2014;44(3):131-138**)

KEY WORDS: Myocardial infarction; Coronary artery disease; Percutaneous coronary intervention.

Introduction

Primary percutaneous coronary intervention (PCI) is a standard interventional treatment modality for managing patients with ST-segment elevation myocardial infarction (STEMI). Remarkable advances in PCI have been made with the development of interventional technologies and the accumulation of experience by interventional cardiologists in patients with acute myocardial infarction (AMI) requiring urgent revascularization. However, several issues can cause difficulties for interventional cardiologists, such as multivessel coronary artery disease (MVD) on a diagnostic coronary angiogram, which is seen in 50–80% of patients.¹⁻⁴ More adverse cardiovascular events occur in patients with MVD than those without MVD, and

a lack of accurate guidelines makes it difficult for cardiologists to determine the extent of revascularization.^{5,6}

Two interventional strategies have been used for managing STEMI with MVD. Infarct-related or culprit vessel-only revascularization (CVR) is an intervention of the infarct-related artery (IRA) only; no other diseased vessels are targeted, regardless of their significance. The other strategy is multivessel revascularization (MVR), defined as an intervention of more than one significant stenotic vessel. It includes treating all diseased vessels, referred to as complete revascularization, and is divided into "staged" (IRA intervention followed by elective second staged non-IRA revascularization) and ad hoc (simultaneous IRA and non-IRA intervention during an index procedure) PCI based on the timing of the non-IRA intervention. The potential disadvantages of multivessel intervention should also be considered, such as the risk of contrast-induced nephropathy, radiation exposure, the development of stent thrombosis or other periprocedural complications, and the risk of ongoing ischemia by remnant lesions.⁷ In addition, cardiogenic shock at initial presentation can affect the PCI strategy in patients with STEMI. There are still limited data on the optimal PCI strategy in patients with MVD presenting with STEMI. This review describes the current status of MVR in STEMI patients based on recently published data and proposes an optimal revascularization strategy.

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Interventional Strategies for ST-Segment Elevation Myocardial Infarction with Multivessel Coronary Artery Disease

The current American College of Cardiology/American Heart Association (ACC/AHA) and European revascularization guidelines for STEMI recommend CVR during primary PCI as the primary interventional strategy in patients with MVD.^{8,9)} Although CVR is a universally accepted treatment modality in STEMI patients, several studies have shown the efficacy of simultaneous IRA and non-IRA intervention during primary ad hoc PCI and a staged PCI procedure.

Infarct-related artery intervention during primary percutaneous coronary intervention

Culprit vessel-only revascularization is an interventional strategy that revascularizes only the IRA during primary PCI, regardless of the significance of non-IRAs. Thus, it is a conservative management approach that allows for revascularization of the IRA only followed by medical therapy, and some studies have shown more favorable outcomes of CVR than MVR during primary PCI.

An early study by Roe et al.¹⁰⁾ described increased 6-month mortality and major adverse cardiac events (MACEs) with MVR. Corpus et al.⁵⁾ analyzed 506 patients with MVD; 152 were treated with MVR and 354 were treated with CVR during primary PCI. MVR was associated with higher rates of re-infarction (13.0% vs. 2.8%, $p < 0.001$), revascularization (25.0% vs. 15.0%, $p = 0.007$), and composite MACE (40.0% vs. 28.0%, $p = 0.006$) compared to CVR after 1-year of clinical follow-up. A recent analysis of the APEX-AMI trial¹¹⁾ examined the incidence of CVR during primary PCI and 90-day outcomes compared to MVR. Among 2210 patients with MVD, only 217 (9.9%) underwent CVR. Death and death/congestive heart failure/shock after 90-days was significantly higher in the MVR group than that in the CVR group (12.5% vs. 5.6%, $p < 0.001$ and 17.4% vs. 12.0%, $p = 0.020$, respectively). Furthermore, MVR was associated with an increased risk of 90-day mortality {adjusted hazard ratio (HR) 2.44; 95% confidence interval (CI), 1.55–3.83; $p < 0.001$ } after adjusting for patient and procedural characteristics, as well as the propensity for MVR. Dziewierz et al.¹²⁾ reported that non-IRA PCI during an index procedure in patients with STEMI and MVD is associated with increased 1-year mortality in a registry database (European Registry on Patients with ST-Elevation MI Transferred for Mechanical Reperfusion with a Special Focus on Upstream Use of Abciximab; EUROTRANSFER).

Recent studies also showed inferior clinical outcomes of MVR compared to patients who received CVR during primary PCI,^{13,14)} and the meta-analysis of Vlaar et al.¹⁵⁾ revealed higher mortality rates of patients who underwent MVR during long-term follow-up com-

pared to CVR or a staged PCI group.

Simultaneous infarct-related and non infarct-related artery intervention during primary percutaneous coronary intervention

Limited data show the benefits of simultaneous IRA and non-IRA intervention during primary PCI. Although several early studies supported the superiority of MVR over CVR, they included only a small number of patients and were not randomized.^{16–18)} Politi et al.¹⁹⁾ performed a randomized trial assessing the outcomes of 214 patients with STEMI and MVD undergoing primary PCI. All patients were randomized before angioplasty into CVR, ad hoc MVR, and staged PCI groups. During a mean follow-up of 2.5 years, there were more MACEs in the CVR group (50% of patients) than those in the MVR (23%) and staged PCI (20%) groups.

Bangalore et al.²⁰⁾ performed a meta-analysis of 61764 subjects with STEMI and MVD in 19 studies with 23 arms, and associated MVR with a 44% decrease in repeat PCI and MACEs {odds ratio (OR), 0.68; 95% CI, 0.57–0.81} for early outcomes within 30 days, despite similar mortality, MI, stroke, and target vessel revascularization. No differences related to MI, target vessel revascularization, or stent thrombosis were observed for long-term outcomes, with a decreased risk of mortality, repeat PCI, coronary artery bypass surgery, and MACE (OR, 0.60; 95% CI, 0.50–0.72) with MVR. However, that study was limited because it was a non-randomized trial that included only two randomized controlled trials in the meta-analysis.

A recent trial by Wald et al.²¹⁾ randomized 465 patients with STEMI who underwent primary PCI into two groups: preventive PCI (234 patients) or no preventive PCI (231 patients). Primary outcomes were composite cardiac deaths, non-fatal MI, and refractory angina. During a mean follow-up of 23 months, primary outcomes occurred more often in the no preventive PCI group (HR, 0.35; $p < 0.001$) and the HRs were 0.34 for cardiac death, 0.32 for non-fatal MI, and 0.35 for refractory angina. They concluded that preventive PCI in non-IRA significantly reduced the risk of MACE compared to CVR in patients with STEMI who underwent primary PCI.

In a large-scale Korean registry (Korea Acute Myocardial Infarction Registry, KAMIR), two recent studies evaluated the efficacy of MVR in patients with STEMI and MVD.^{22,23)} Jo et al.²²⁾ analyzed 1094 STEMI patients with MVD who underwent primary PCI with drug-eluting stents (827 in the CVR and 267 in the MVR groups). During a 1-year follow-up, MACE rates were similar in the CVR (15.2%) and MVR (14.2%) groups, despite higher in-hospital mortality in the CVR group (5.2% vs. 0.4%, $p < 0.001$). In subgroup analyses between complete ($n = 182$) and incomplete ($n = 912$) revascularized patients, the former had a lower 1-year MACE rate (9.5% vs. 15.0%, $p = 0.039$) primarily driven by the non-target vessel repeat PCI rate (1.8% vs. 8.6%, $p = 0.002$). They concluded that MVR for STEMI showed similar 1-year

MACE compared to CVR. However, complete revascularization was associated with a lower rate of non-target vessel repeat revascularization during the follow-up period after multivessel PCI in subgroup analyses. Lee et al.²³⁾ also compared CVR (1106 patients) with MVR (538 patients) in 1644 STEMI and MVD patients who received primary PCI using stent implantation or balloon angioplasty. In-hospital outcomes such as mortality, complications, acute kidney injury, major bleeding, and new onset heart failure were similar between the two groups, except for the development of fatal ventricular arrhythmia (4.5% vs. 2.4%, $p=0.037$). At 1 month, the occurrence of MACE was not different between the two groups. The MACE rate at 1 year was also similar between both groups; however, the target-lesion repeat PCI rate was higher in the MVR group (2.4% vs. 5.9%, $p<0.0001$). Therefore, they concluded that there were no significant differences in clinical outcomes between the groups, except for a higher risk of target lesion revascularization in the MVR group. These two KAMIR studies showed similar results in that MVR was not superior to CVR in patients with STEMI and MVD. However, the 1-year repeat target-lesion PCI rate was higher in the MVR group in the latter study, which might be associated with a higher proportion of bare-metal stents implanted in the study population (8.7% in the CVR group and 11.0% in the MVR group), as well as other angiographic factors. However, limited information on staged PCI and a lack of detailed angiographic anatomies in these studies may have underestimated the outcomes.

Although some studies have shown superiority of MVR in patients with STEMI, the results have been limited by changes in standard interventional strategies of primary PCI. Thus, further investigation is needed.

Staged percutaneous coronary intervention: infarct-related artery intervention followed by non-infarct-related intervention as a staged procedure

Although there is no definitive evidence that MVR is superior to CVR, and the current guidelines support CVR during primary PCI, several recent studies have suggested that staged multivessel PCI can be an alternative interventional strategy to achieve optimal clinical outcomes. Hannan et al.¹³⁾ showed that culprit vessel PCI during the index procedure for patients without hemodynamic compromise is associated with lower in-hospital mortality than multivessel PCI during the index procedure (0.9% vs. 2.4%, $p=0.04$). Interestingly, patients who underwent staged multivessel PCI within 60 days after the index procedure had a significantly lower 12-month mortality rate than those who underwent culprit vessel PCI only (1.3% vs. 3.3%, $p=0.04$).

Vlaar et al.¹⁵⁾ performed a meta-analysis including four prospective and 14 retrospective studies involving 40280 patients. Their

analysis favored a staged PCI strategy with complete revascularization. Among different interventional strategy groups, staged PCI was associated with lower short- and long-term mortality compared to CVR and ad hoc MVR, and the MVR group showed the highest mortality rates at both short- and long-term follow-ups. Another study supported the use of staged PCI. A subgroup analysis in the Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction trial (HORIZONS-AMI)²⁴⁾ compared CVR to staged PCI; the results indicated higher 1-year mortality (9.2% vs. 2.3%; HR, 4.10), cardiac death (6.2% vs. 2.0%; HR, 3.14), and stent thrombosis (5.7% vs. 2.3%; HR, 2.49) in the CVR group than those in the staged PCI group. Furthermore, there was a trend toward higher 1-year adverse cardiac events (18.1% vs. 13.4%; HR 1.42; $p=0.08$) in the former group.

Jensen et al.²⁵⁾ also reported that staged multivessel PCI within 60 days after index hospitalization can reduce 1-year mortality compared to patients who undergo CVR during primary PCI (HR, 0.28; 95% CI, 0.14–0.54). Taken together, these results indicate that staged PCI is promising, and another large randomized trial such as the Complete Versus Culprit-Lesion Only Primary PCI Trial (CVLPRIT) may provide more valuable information.²⁶⁾ These STEMI studies are summarized in Table 1.

Optimal Interventional Strategy in Patients with Multivessel Coronary Artery Disease Complicating Cardiogenic Shock

Although current guidelines recommend CVR during primary PCI in patients with STEMI, MVR can be selected when STEMI patients initially present in cardiogenic shock that is primarily associated with STEMI. Thus, studies regarding MVD and shock with AMI have reported this issue in STEMI patients.²⁷⁾

Several studies of MVR in STEMI patients complicated by cardiogenic shock have demonstrated no additional benefit of MVR in this circumstance. Cavender et al.¹⁴⁾ analyzed patients with STEMI and cardiogenic shock in the National Cardiovascular Data Registry ($n=3087$) and showed that those who received MVR during primary PCI had greater in-hospital mortality than that of patients that received CVR (36.5% vs. 27.8%; OR, 1.54; 95% CI, 1.22–1.95). These data suggest that performing MVR during primary PCI for STEMI does not improve short-term survival, even for patients with cardiogenic shock and at-risk for increased mortality due to procedural-related complications, such as bleeding or renal failure, distal embolization associated with PCI, or the loss of collateral flow to other coronary territories.²⁸⁾²⁹⁾ Bauer et al.³⁰⁾ evaluated the impact of MVR on in-hospital outcomes of 336 AMI patients with MVD presenting with cardiogenic shock in the Euro Heart Survey PCI registry. The

Table 1. Publications regarding multivessel percutaneous coronary intervention in ST-segment elevation myocardial infarction (except for meta-analyses)

	Multivessel PCI group (n)	Culprit-only PCI Group (n)	Primary outcome	Main findings
Studies showed non-association of multivessel PCI with improved clinical outcomes				
Roe et al. ¹⁰⁾	79	79	Death, re-infarction and stroke	High incidence of stroke (10.3% vs. 0%, p<0.001)
Corpus et al. ⁵⁾	152	354	MACE	40% vs. 28%, p=0.006
Toma et al. ¹¹⁾	217	1984	90-day mortality	HR 2.4 (1.6 to 3.8), p<0.001 for multivessel PCI group
Dziewierz et al. ¹²⁾	70	707	1-year mortality	OR 2.0 (0.9 to 4.7), p=0.09
Cavender et al. ¹⁴⁾	3134	25802	In-hospital mortality	7.9% vs. 5.1%, p<0.01
Studies showed superiority of multivessel PCI				
Qarawani et al. ¹⁶⁾	95	25	MACE	16.7% vs. 52%, p=0.0001
Rigattieri et al. ¹⁷⁾	64	46	MACE (out-of-hospital)	9.3% vs. 23.9%, p=0.037
Varani et al. ¹⁸⁾	243	159	30-day mortality (exclude shock patients)	2.8% vs. 6.3%, p=0.023
Politi et al. ¹⁹⁾	130	84	MACE	20.7% vs. 50%, p<0.001
Wald et al. ²¹⁾	234	231	Cardiac death, nonfatal MI, and refractory angina	HR 0.3 (0.1 to 1.1)
Jo et al. ²²⁾	267	827	Death, MI, TVR and non-TVR	High incidence of non-TVR (8.6% vs. 1.8%, p=0.002)
Lee et al. ²³⁾	538	1106	MACE	OR 1.1 (0.7% to 1.8), p=0.711
Studies showed superiority of staged multivessel PCI				
Hannan et al. ¹³⁾	797 (staged PCI)	2724	1-year mortality	1.3% vs. 3.3%, p=0.04
Kornowski et al. ²⁴⁾	393 (staged PCI)	275	1-year mortality	2.3% vs. 9.2%, p<0.0001
Jensen et al. ²⁵⁾	626 (staged PCI within 60 days after index hospitalization)	4770	1-year mortality	HR 0.3 (0.1 to 0.5) for staged PCI

PCI: percutaneous coronary intervention, MACE: major adverse cardiac events, HR: hazard ratio, OR: odds ratio, MI: myocardial infarction, TVR: target-vessel revascularization

prevalence of three-vessel disease (60% vs. 57%), presentation with resuscitation (48% vs. 46%), and STEMI (83% vs. 87%) were similar between the two patient groups who received another interventional strategy when MVR and CVR were compared. After adjusting for confounding factors, an additional non-culprit PCI was not associated with an in-hospital survival benefit (OR, 1.28, 95% CI, 0.72–2.28, p=0.07) in these high-risk patients. In a recent Korean study, Yang et al.³¹⁾ reported that MVR did not reduce the prevalence of mortality in patients with cardiogenic shock complicating STEMI and MVD during primary PCI.

A recent French study on the role of MVR in patients with STEMI presenting with cardiogenic shock and resuscitated cardiac arrest showed that MVR may improve 6-month survival rate.³²⁾ However, these results cannot be generalized until results are reported from a randomized controlled trial. Current 2010 ESC/EACTS myocardial revascularization guidelines state that MVR during primary PCI can be justified only in hemodynamically unstable patients with multiple truly critical lesions,³³⁾ and this interventional strategy is still an ef-

fective modality in these patients.

Real-World Application of Multivessel Intervention in Patients with ST-Segment Elevation Myocardial Infarction

The results described above are heterogeneous and thus inconclusive regarding applications in real-world practice. Multivessel PCI has advantages and disadvantages, as described by Widimsky and Holmes (Table 2).⁷⁾ The following factors should be considered before determining the interventional strategy.

First, in patients with STEMI and MVD, CVR is still an effective interventional strategy during primary PCI in hemodynamically stable patients, as recommended by the current guidelines. A recent meta-analysis by Bagai et al.³⁴⁾ analyzed outcomes of MVR compared to CVR during primary PCI in 14 studies composed of 11 cohort and three randomized controlled trials. The MVR group had more patients in cardiogenic shock and with an anterior infarction. Although

Table 2. The advantages and disadvantages of each interventional strategy in patients with acute myocardial infarction

	Advantages	Disadvantages
Multivessel revascularization during index procedure ("ad hoc" PCI)	Patients preference Stabilize other unstable lesions	Increased risk of contrast-induced nephropathy Increased dosage of radiation Increased risk of periprocedural complications Increased risk of stent thrombosis
Culprit-only revascularization	Low incidence of periprocedural complications	Risk of recurrent angina Risk of remnant unstable lesions
Staged multivessel revascularization	Treat secondary lesions more safely Functional assessment before secondary PCI	Economic problem Uncertain timing for secondary PCI Possibility for unnecessary treat

PCI: percutaneous coronary intervention

short- and long-term MACE occurred more often in the MVR group, the primary endpoint was similar after excluding patients with shock in analyses limited to randomized controlled trials. Another small study reported similar results and risk profiles of patients undergoing MVR during primary PCI.³⁵⁾ Because there may be selection bias in non-randomized trials that compare MVR and CVR, more randomized controlled trials are needed to confirm these conclusions.

Second, CVR is also an effective interventional strategy during primary PCI in patients with hemodynamically unstable STEMI. Several studies that compared MVR to CVR during primary PCI in patients in cardiogenic shock did not demonstrate any advantage to MVR. One prospective observational study described that MVR primary PCI in STEMI patients with MVD presenting with cardiogenic shock and resuscitated cardiac arrest improved short-term mortality.³²⁾ MVR during primary PCI in patients with STEMI and MVD should be selected in patients in a hemodynamically unstable state with multiple critical coronary stenoses.

Third, staged PCI is highly recommended in patients who receive CVR during primary PCI. Several reports and a recent randomized controlled trial have shown promising results with this strategy. However, it remains to be determined whether complete or incomplete revascularization, non-IRA intervention, and timing of intervention can be improved. Although recent studies have supported complete revascularization in patients, including those with angina,³⁶⁻³⁸⁾ more studies are needed to establish staged PCI in these patients.

However, different clinical scenarios in a real-world setting cause hardship when applying these literature-based interventional strategies. Dangas et al.³⁹⁾ surveyed this issue based on the opinions of interventional cardiology experts. About 80% of interventional cardiologists are consistent in their recommendation to elect second staged PCI in case of STEMI patients with MVD with a concurrent significant proximal lesion in a nonculprit vessel who are hemodynamically stable after primary PCI. Many factors such as renal function, accumulated contrast use, lesion complexity, symptomatology,

radiation dose, left ventricular function, insurance status, and patient age influenced their decisions. The decision making for PCI in patients with STEMI and MVD should be individualized according to the clinical situation.

There are several considerations that need to be made prior to non-IRA intervention to assist decision making for multivessel PCI. The adequacy of the intervention should be compared to coronary artery bypass graft (CABG) surgery based on clinical benefits in patients with MVD. The current ACC/AHA guidelines recommend CABG (class I indication, level of evidence: A) in patients with MVD according to the complexity of the coronary anatomy, such as three-vessel disease or left main coronary artery disease or two-vessel disease with significant proximal left anterior descending coronary artery disease and abnormal left ventricular dysfunction. However, it is difficult to recommend CABG based on the guidelines in all patients indicated for surgery because of advanced age, co-morbidities, and the high complication rate of CABG. The "synergy between PCI with Taxus™ and cardiac surgery" (SYNTAX) score was designed to predict outcomes related to anatomical characteristics such as the dominant artery, number of lesions, other lesion characteristics, and, to a lesser extent, the functional risk of occlusion of any coronary artery segment in patients with MVD.⁴⁰⁾ A high SYNTAX score indicates the most complex disease. In the SYNTAX trial,⁴¹⁾ patients with a high SYNTAX score (>33 points) who underwent PCI showed poorer cardiovascular outcomes compared to those who underwent CABG. Although this scoring system cannot be applied to all patients with MVD, it may be helpful for determining whether PCI or surgery is better in individual patients. A functional assessment of myocardial viability is also crucial for reducing unnecessary revascularization of non-IRA. Dobutamine echocardiography⁴²⁾ and myocardial nuclear imaging, such as single photon emission tomography or positron emission tomography,⁴³⁾ are well-known modalities used to evaluate myocardial viability. Cardiac magnetic resonance imaging (CMRI) has increasingly been performed to accurately predict infarct size, regional wall motion abnormalities, ejection frac-

tion, and myocardial irreversibility.^{44,45} In addition, CMRI can predict functional recovery of the left ventricle after PCI.⁴⁶ However, because there are no available data on the clinical benefits of CMRI-guided intervention for assessing the significance of non-IRA, the fractional flow reserve (FFR) procedure is practical for determining the level of ischemia using a pressure wire. The Fractional Flow Reserve Versus Angiograph for Multivessel Evaluation (FAME) study was a randomized, prospective, multicenter trial that investigated the benefits of FFR-guided PCI. This technique was associated with lesser stent implantation, less injection of contrast, and a reduction in adverse cardiac events, death, or myocardial infarction.⁴⁷⁻⁴⁹ This remarkable result supports the active use of FFR for assessing ischemia during intermediate coronary stenosis. Moreover, FFR costs less compared to angiography-guided PCI.⁵⁰

Conclusions

Based on the current literature, the optimal revascularization strategy for STEMI patients with MVD remains controversial. Assessment of myocardial viability and a functional evaluation of myocardial perfusion are essential before non-IRA intervention. Current guidelines supporting CVR during primary PCI as a default strategy may impact initial management, and ad hoc PCI should be carefully performed only in hemodynamically unstable patients. Promising results for staged PCI in STEMI patients with MVD suggest that this strategy should be considered before other methods. However, patients with MVD have more co-morbidities and are generally elderly. Thus, individualization of treatments and a consideration of the advantages or disadvantages of the intervention remain important. Further large-scale, randomized, controlled trials are necessary to establish the optimal revascularization strategy for these high-risk patients.

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