



Timing of fractional flow reserve-guided complete revascularization in patients with ST-segment elevation myocardial infarction with multivessel disease: Rationale and design of the OPTION-STEMI trial

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ABSTRACT

Background Current guidelines recommend complete revascularization (CR) in hemodynamically stable patients with ST-segment elevation myocardial infarction (STEMI) and multivessel coronary artery disease (MVD). With regard to the timing of percutaneous coronary intervention (PCI) for non-infarct-related artery (non-IRA), recent randomized clinical trials have revealed that immediate CR was non-inferior to staged CR. However, the optimal timing of CR remains uncertain. The OPTION-STEMI trial compared immediate CR and in-hospital staged CR guided by fractional flow reserve (FFR) for intermediate stenosis of the non-IRA.

Methods The OPTION-STEMI is a multicenter, investigator-initiated, prospective, open-label, non-inferiority randomized clinical trial. The study included patients with at least 1 non-IRA lesion with $\geq 50\%$ stenosis by visual estimation. Patients fulfilling the inclusion criteria were randomized into 2 groups at a 1:1 ratio: immediate CR (i.e., PCI for the non-IRA performed during primary angioplasty) or in-hospital staged CR. In the in-hospital staged CR group, PCI for non-IRA lesions was performed on another day during the index hospitalization. Non-IRA lesions with 50%–69% stenosis by visual estimation were evaluated by FFR, whereas those with $\geq 70\%$ stenosis was revascularized without FFR. The primary endpoint was the composite of

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all-cause death, non-fatal myocardial infarction, and all unplanned revascularization at 1 year after randomization. Enrolment began in December 2019 and was completed in January 2024. The follow-up for the primary endpoint will be completed in January 2025, and primary results will be available in the middle of 2025.

Conclusions The OPTION-STEMI is a multicenter, non-inferiority, randomized trial that evaluated the timing of in-hospital CR with the aid of FFR in patients with STEMI and MVD.

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Background

Multivessel coronary artery disease (MVD) is a common clinical condition, affecting almost half of all patients with ST-segment elevation myocardial infarction (STEMI). It is associated with worse clinical outcomes than single-vessel disease.^{1,2} Current guidelines and randomized clinical trials recommend complete revascularization (CR) in patients with STEMI and MVD.^{3,4} CR during primary angioplasty or in a staged manner has several advantages compared to culprit-vessel only revascularization.^{5,7} Furthermore, fractional flow reserve (FFR)-guided percutaneous coronary intervention (PCI) for the non-infarct-related artery (non-IRA) was more effective than angiography-guided PCI of the non-IRA for reducing need for repeat revascularization.^{8,9}

There has been concern regarding the timing of PCI for the non-IRA following primary PCI. Although current guidelines recommend CR based on the results of the aforementioned randomized trials, they have not made recommendations for the timing of CR. These guidelines suggest that CR should be performed during primary angioplasty or in a staged manner during initial hospitalization or after discharge.^{3,4} Recently, 2 large-scale randomized clinical trials regarding the timing of CR revealed that immediate CR was non-inferior to staged CR in patients with acute coronary syndrome or STEMI and MVD.^{10,11} However, these trials have certain limitations, such as the long interval between randomization and non-IRA PCI and the lack of routine use of FFR guidance for the non-IRA. Although FFR is widely used to evaluate significant ischemia due to moderate stenosis, most previous studies evaluating FFR have not enrolled patients with acute myocardial infarction (AMI).^{12,13} FFR is reliable in the acute-to-stable stages of AMI, and several recent randomized trials have used FFR guidance for the non-IRA, revealing that it is safe in patients with AMI and MVD.^{14,17}

Therefore, we designed a large-scale randomized trial to investigate the optimal timing of in-hospital CR with the aid of FFR. The **Optimal Timing of Fractional Flow Reserve-Guided Complete Revascularization ON for Non-Infarct-Related Artery in ST-Segment Elevation Myocardial Infarction with Multivessel Dis-**

ease (OPTION-STEMI) trial is a multicenter, investigator-initiated, prospective, open-label, non-inferiority randomized clinical trial comparing immediate CR during primary PCI and in-hospital staged CR under FFR guidance for intermediate stenosis of the non-IRA in patients with STEMI and MVD.

Methods

Study overview

The OPTION-STEMI is a multicenter, investigator-initiated, prospective, open-label, non-inferiority randomized clinical trial. The primary aim of this trial was to determine the optimal timing of in-hospital CR with the aid of FFR in hemodynamically stable patients with STEMI and MVD. The primary analysis focused on evaluating non-inferiority. The trial protocol was approved by the Institutional Review Board of each participating center. The study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization, and Good Clinical Practice guidelines. The trial was registered at ClinicalTrials.gov (NCT04626882). At the time of registration, the trial had already begun patient enrolment. However, before enrolment of the first patient, the trial was registered at the Clinical Research Information Service (www.cris.nih.go.kr), a non-profit online registration system for clinical trials to be conducted in Korea (KCT0004457). This registry is a part of the WHO International Clinical Trials Registration Platform (www.who.int/clinical-trials-registry-platform/network/primary-registries).

Study participants

Table 1 presents the study eligibility criteria. Patients with STEMI and MVD were screened and randomized following successful PCI for IRA. Latecomers with ischemic symptom onset >12 h ago were excluded. MVD was defined as at least one non-IRA with diameter ≥ 2.5 mm and 50% stenosis by visual estimation. Patients with chronic total occlusion at the non-IRA, as well as those with unprotected left main coronary artery disease with $\geq 50\%$ stenosis, initial thrombolysis in myocardial infarction (TIMI) flow at the non-IRA ≤ 2 , or cardiogenic shock

Table 1. Inclusion and exclusion criteria.

Inclusion criteria

1. Age ≥ 19 years
2. ST-segment elevation myocardial infarction
 - 1) ST-segment elevation ≥ 0.1 mV in at least 2 contiguous leads or,
 - 2) New onset left bundle branch block
3. Primary PCI within 12 hours after symptom development
4. Multivessel disease: Non-IRA with diameter ≥ 2.5 mm and 50% stenosis by visual estimation
5. Patient's or guardian's consent after understanding the study

Exclusion criteria

1. Cardiogenic shock at initial presentation or after IRA treatment
2. Unprotected left main coronary artery disease with $\geq 50\%$ stenosis by visual estimation
3. TIMI flow at non-IRA ≤ 2
4. Severe procedural complications as judged by operators
5. Non-IRA lesion not suitable for PCI treatment as judged by operators
6. Chronic total occlusion at non-IRA
7. History of anaphylaxis to contrast agent
8. Pregnancy and lactation
9. Life expectancy < 1 year
10. Severe valvular disease
11. History of CABG, or planned CABG
12. Fibrinolysis before admission
13. Severe asthma
14. Patient's refusal to participate in study

Abbreviations: CABG, coronary artery bypass grafting; IRA, infarct-related artery; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction.

at initial presentation or after IRA treatment were excluded. Patients with a non-IRA that was unsuitable for PCI and those with severe procedural complications were considered ineligible, as per the operators' discretion.

Following successful PCI for IRA, written informed consent was obtained from patients or their legal representatives if the patient was unable to provide consent at the end of the primary PCI for IRA. In cases where consent was obtained from legal representatives, informed consent was also obtained from patients after they have been stabilized. Patients were not enrolled until informed consent was obtained from themselves or their legal representatives.

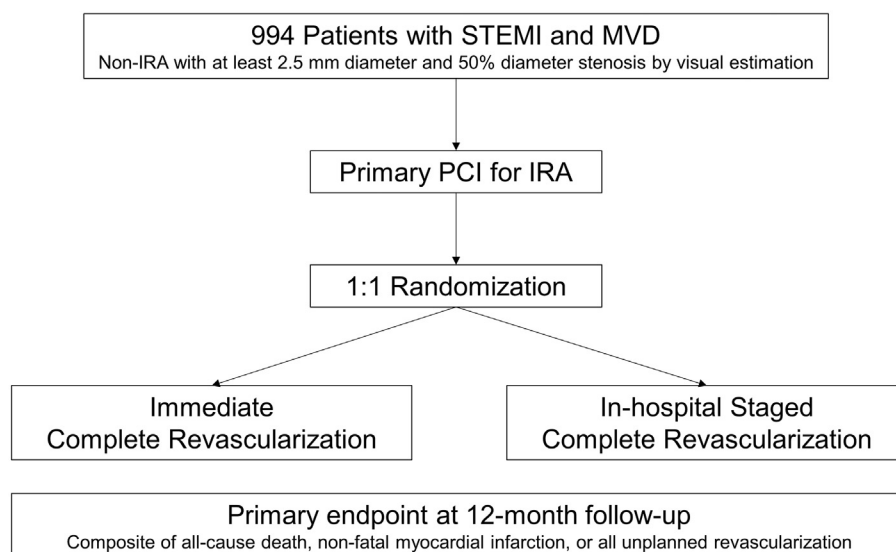
Randomization and study intervention

Patients were randomized at a 1:1 ratio to the immediate CR during primary PCI or in-hospital staged CR group (Figure 1). Randomization was performed based on randomly permuted blocks of various sizes using a web-based randomization system (<https://ecrf.kr/optionstemi>) developed by an independent organization (TnW Software, Seoul, Korea). Successful PCI for IRA was considered as reduction of minimum stenosis $< 20\%$ on angiography in the presence of TIMI grade 2 or 3 flow. In the immediate CR group, revascularization for the non-IRA was performed during the index procedure immediately following PCI for IRA. However, in the in-hospital staged CR group, revascularization for the non-IRA was performed on another day during hospitalization. PCI for the non-IRA was performed as soon as possible unless necessary, such as in cases of renal insufficiency. In both

groups, non-IRA lesions with stenosis $\geq 70\%$ by visual estimation were revascularized without FFR. Conversely, FFR was evaluated for non-IRA lesions with 50%–69% stenosis using a pressure-sensor guide wire (Abbott Vascular, Santa Clara, CA, USA; Philips Volcano, San Diego, CA, USA). Subsequently, PCI was performed for lesions with FFR ≤ 0.80 . During FFR, hyperemia was induced by intravascular infusion of adenosine (140 $\mu\text{g/kg/min}$) or intracoronary nicorandil (bolus of 2 mg).¹⁸

PCI was performed for both the IRA and non-IRA using everolimus-eluting stents with a bioabsorbable polymer (Synergy; Boston Scientific, Marlborough, MA, USA), drug-coated balloon, or standard balloon angioplasty. We did not exclude patients with stent thrombosis presenting with STEMI in this trial. In these patients, additional stent may not be needed in the majority of cases. Furthermore, we think that drug-coated balloon is an alternative option to treat lesions which are distally located or with small diameter. However, we think that the usage rate of drug-coated balloon and balloon angioplasty only will be very low. The usage rate of drug-coated balloon was 0.7% in the FRAME-AMI (fractional flow reserve vs. angiography-guided strategy for management of non-infarction related artery stenosis in patients with acute myocardial infarction) trial which compared angio- and FFR-guided PCI for AMI and multivessel disease, and no one treated with balloon angioplasty only in that trial.¹⁵ Medical treatment was administered to all participants according to the guidelines. Furthermore, dual antiplatelet therapy was continued for at least 12 months.^{19,20} The choice of P2Y₁₂ inhibitor (clopidogrel, prasugrel, or ticagrelor), vascular access site, thrombus

Figure 1. Study flow chart of the OPTION-STEMI trial. Abbreviations: IRA, infarct-related artery; MVD, multivessel disease; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.



aspiration device, glycoprotein IIb/IIIa inhibitor, and intravascular imaging, such as intravascular ultrasound or optical coherence tomography, was at the operators' discretion. Left ventricular ejection fraction was assessed by transthoracic echocardiography during hospitalization.

Study measurements

The following data were collected at the time of randomization or during hospitalization: age, sex, body mass index, comorbidities, blood pressure, heart rate, infarct location on 12-lead electrocardiogram, Killip class, left ventricular ejection fraction, laboratory findings, discharge medications, complications during hospitalization, and length of hospital stay.

The following procedure-related data were also collected: symptom-to-balloon time, door-to-balloon time, number of diseased arteries, PCI characteristics for both the IRA and non-IRA (location of the IRA or non-IRA, vascular access, lesion location, number of lesions, pre-procedure quantitative coronary angiography data [reference vessel diameter, minimum lumen diameter, diameter stenosis, and lesion length], post-procedure quantitative coronary angiography data [diameter stenosis], ACC/AHA lesion type, pre- and post-TIMI flow grade, thrombus aspiration, use of glycoprotein IIb/IIIa inhibitor, treatment method [balloon angioplasty only, drug-eluting stent, or drug-coated balloon angioplasty], use of intravascular imaging, number of stents, stent diameter and length, and time to staged procedure in the in-hospital CR group). FFR characteristics (FFR measurement, mean FFR value, $\text{FFR} > 0.80$, $\text{FFR} \leq 0.80$, no FFR measurement due to stenosis $\geq 70\%$ by visual assess-

ment), baseline and residual SYNTAX (SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery) score, and contrast amount/fluoroscopic time/radiation dose (index, staged procedure, and total quantity).

Study endpoints

Table 2 presents the study endpoints. The primary endpoint is the cumulative incidence of a composite of all-cause death, non-fatal myocardial infarction, and all unplanned revascularization at 1 year after randomization. The secondary endpoints include the individual components of the primary endpoint, target lesion revascularization, target vessel revascularization, non-target vessel revascularization, cardiac death, non-cardiac death, hospitalization for unstable angina, hospitalization for heart failure, definite or probable stent thrombosis, stroke, major bleeding by the Bleeding Academic Research Consortium, and contrast-induced nephropathy. Although short-term outcomes are important in this trial because CR is achieved during initial admission in the OPTION-STEMI trial contrary to BIOVASC (percutaneous complete revascularization strategies using sirolimus-eluting biodegradable polymer-coated stents in patients presenting with acute coronary syndrome and multivessel disease) and MULTISTARS AMI (MULTi-vessel Immediate versus STaged Revascularization in Acute Myocardial Infarction) trials, study endpoints had occurred continuously within 1 year despite the achievement of CR in BIOVASC and MULTISTARS trials. Furthermore, long-term event rate up to 5 years is not low after achievement of CR in the 5-year results of the CvLPRIT (Complete versus

Table 2. Primary and secondary endpoints.

Primary endpoint

- A composite of all-cause death, non-fatal MI, or all unplanned revascularization at 1 year after randomization

Secondary endpoints

- All unplanned revascularization
- Target-lesion revascularization
- Target-vessel revascularization
- Non-target vessel revascularization
- All-cause death
- Cardiac death
- Non-cardiac death
- Non-fatal MI
- Hospitalization for unstable angina
- Hospitalization for heart failure
- Definite or probable stent thrombosis
- Stroke
- Major bleeding by BARC classification
- Contrast-induced nephropathy

Abbreviations: BARC, Bleeding Academic Research Consortium; MI, myocardial infarction.

Lesion-only Primary PCI Trial) trial.²¹ Therefore, we set a follow-up period for the primary endpoint as 1 year similar to other trials regarding STEMI and MVD. We will also examine study endpoints at 1, 6, 24, 36, 48, and 60 months for the short- and long-term clinical outcomes. Supplementary File 1 presents the study endpoints. All primary and secondary endpoints were independently adjudicated by a clinical events committee (CEC) blinded to the group assignments.

Clinical follow-up will be performed with office visits or telephone calls at 1, 6, and 12 months and annually thereafter. The schedule of visits and measurements is provided in Supplementary File 2.

Statistical methods

The incidence of a composite of all-cause death, non-fatal myocardial infarction or repeat revascularization at 1 year was 13.4% in the Korean nationwide study, 7.8% in the FFR-guided CR group in the COMPARE-ACUTE (Comparison between FFR guided revascularization versus conventional strategy in acute STEMI Patients With MVD) trial and 6.5% in the FFR-guided CR group in the DANAMI3-PRIMULTI (primary PCI in patients With ST-elevation myocardial infarction and multivessel disease: treatment of culprit lesion only or complete revascularization) trial.^{8,9,22} Based on the results of aforementioned studies, we assumed a 12-month rate of the primary composite endpoint of 10.5% in the in-hospital staged CR group. The non-inferiority margin for the hazard ratio was 1.42, selected based on clinical judgement and contemporary trials of FFR-guided PCI.^{23,24} Although a non-inferiority margin for hazard ratio of 1.43 seems to be large in this trial, the majority of non-inferiority trials including device and pharmacologic trials set a non-inferiority margin as a more than 1.40.²⁵ Furthermore,

the non-inferiority margin of the BIOVASC and MULTI-STARs AMI trial was 1.39 and 1.46, respectively. Therefore, we thought that a non-inferior margin for hazard ratio of 1.42, which was equivalent to a 4.4% increase in the expected event rate was clinically acceptable. We assumed that an accrual time of 4 years and follow-up of 1 year for the primary outcome were needed. Thus, we estimated that 994 patients would be needed to achieve a power of 80%, one-sided type I error rate of 0.025, and dropout rate of 4%. The sample size was evaluated using PASS 16 software (NCSS, Kaysville, UT, USA).

Baseline and procedure-related characteristics will be analyzed for both treatment groups. Continuous variables are presented as means±SD or medians (IQRs) as appropriate. If variables are normally distributed, the variables will be compared using Student's t-test; otherwise, they will be compared using the Mann-Whitney U test. Categorical variables will be presented as frequencies with percentages and compared using the chi-square or Fisher's exact test as appropriate. The primary endpoint will be analyzed on an intention-to-treat basis. The cumulative event rate of the primary endpoint will be estimated using the Kaplan-Meier method and compared using log-rank tests. In the Cox proportional hazard model, the hazard ratio for immediate CR compared to in-hospital staged CR will be assessed for non-inferiority. If the upper limit of the one-sided 97.5% confidence interval of the hazard ratio is less than the prespecified non-inferiority margin of 1.42, immediate CR will be considered non-inferior to in-hospital staged CR. If the non-inferiority criteria are fulfilled, superiority will also be tested. Additional sensitivity analysis will be performed in the per-protocol population. Secondary endpoints will be analyzed using the Kaplan-Meier method with the log-rank test and Cox proportional

hazard model. Cumulative event rates of study endpoints will be estimated using the Kaplan–Meier method and compared using log-rank tests. The occurrence of contrast-induced nephropathy will be analyzed using the chi-square test. *P*-values <.05 will be considered indicative of statistical significance. Cox proportional hazard models with an interaction test will be used for subgroup analyses of the primary endpoint according to age (<65 or ≥65 years), sex (male or female), Killip class (I or ≥II), diabetes mellitus (yes or no), number of diseased arteries (2 or 3), left ventricular ejection fraction (<45% or ≥45%), IRA distribution (LAD or non-LAD), and type of P2Y12 inhibitor (clopidogrel, prasugrel, or ticagrelor).

Study organization

The study organization includes an executive committee (EC), a data safety monitoring board (DSMB), and a CEC. The EC is responsible for the study design, protocol, and management. Safety data, including those collected during follow-up, will be independently reviewed by the DSMB for serious adverse events and protocol deviations. The DSMB, consisting of 3 cardiologists, will meet every 6 months after the start of the study and in cases of safety issues. The study protocol, definitions, and endpoints were discussed in the first DSMB meeting. The DSMB chairperson informed the EC regarding any safety issues. All primary and secondary endpoints will be independently adjudicated by the CEC, who will be blinded to the group assignments. The CEC will meet regularly to review and adjudicate all clinical events for which the required minimum data are available.

The OPTION-STEMI trial is an investigator-initiated trial funded by Boston Scientific (Marlborough, MA, USA). The funder has no role in study design, data collection, data management, data analysis, or manuscript writing. The authors are solely responsible for the study design and conduct, data analysis and interpretation, and manuscript publication and final content.

Current status of the trial

Between 30 December 2019 and 15 January 2024, 994 patients were enrolled at the 14 participating sites in Korea. The follow-up of the last enrolled patient will be finished in January 2025. The primary results of this trial are anticipated to be available in the middle of 2025.

Discussion

Recent guidelines for acute coronary syndrome recommend CR in patients with STEMI and MVD, irrespective of the timing of PCI at the non-IRA, based on the results of randomized clinical trials.^{5–9} In addition, 2 large-scale randomized clinical trials revealed the non-inferiority of immediate CR compared to staged CR.^{10,11} However, certain issues still remain, such as how to identify lesions that can be targeted by PCI (e.g., angiography-

or physiology-guided) and when to treat the non-IRA in the staged strategy (e.g., performed in-hospital or electively after discharge).²⁶ The OPTION-STEMI trial investigated whether immediate CR is non-inferior to in-hospital staged CR in patients with STEMI and MVD. In contrast to recently published randomized trials,^{10,11} staged PCI for the non-IRA was performed during hospitalization in the OPTION-STEMI trial. Furthermore, all non-IRA lesions with intermediate stenosis were evaluated using FFR (Table 3).

Timing of staged PCI of the non-IRA: Performed in-hospital or electively after discharge

The post-hoc analysis of the Complete vs. Culprit-Only Revascularization Strategies to Treat Multivessel Disease after Early PCI for STEMI (COMPLETE) trial revealed the benefits of CR over culprit-only PCI, irrespective of the timing of PCI for the non-IRA, i.e., during or after the index hospitalization.²⁷ However, there is uncertainty because the timing for non-IRA PCI was at the discretion of operators in the aforementioned study. In the BIOVASC trial, the timing of staged PCI was planned to be within 6 weeks after the index PCI (during hospitalization or after discharge). Furthermore, the median time to staged procedure was 15 days (interquartile range: 4–28 days).¹⁰ In the MULTISTARS AMI trial, the staged procedure was performed within 19–45 days after the index procedure, with a median time to staged procedure of 37 days (interquartile range: 30–43 days).¹¹ Notably, both unplanned ischemia-driven revascularization and non-fatal MI occurred more frequently in the staged CR group compared to the immediate CR group in both trials.^{10,11} These results might be attributable to the untreated unstable lesion of the non-IRA. Theoretically, there is a risk of progression of a non-IRA lesion if the interval between the index PCI and staged PCI of the non-IRA is long as the plaque instability in AMI may not be limited to the culprit lesion.^{28,29} However, there were no exact data for time to endpoint occurrence in the BIOVASC and MULTISTARS AMI trials, the events seemed to be more occurred in the staged group during the early phase after randomization. Therefore, we think there is a possibility for occurrence of study endpoint related to untreated non-IRA lesions in the very first day. However, the event rate in untreated non-IRA will be minimized in the OPTION-STEMI trial considering the relatively short time to PCI for non-IRA in the in-hospital staged CR and the fact that events in the BIOVASC and MULTISTARS AMI trials were mostly derived from untreated non-IRA lesions. In the OPTION-STEMI trial, the comparison between immediate CR and in-hospital staged CR will provide us with additional information related to the optimal timing of CR.

FFR guidance for non-IRA lesions before PCI

In the OPTION-STEMI trial, the use of FFR was mandatory for intermediate lesions with 50%–69% stenosis

Table 3. Summary of OPTION-STEMI trial and recently published randomized clinical trials.

Trials	OPTION-STEMI (NCT04626882)	BIOVASC ¹⁰ (NCT03621501)	MULTISTARS AMI ¹¹ (NCT03135275)
Study population	STEMI	ACS	STEMI
No. of patients	994	1,525 (606 patients with STEMI)	840
Treatment strategy	Immediate CR	Immediate CR	Immediate CR
Comparator	In-hospital staged CR	Staged CR within 6 weeks after index procedure	Staged CR within 19-45 days after index procedure
Guidance of FFR for non-IRA	All lesion with 50-69% diameter stenosis by visual estimation	Operator's discretion	Operator's discretion
Hypothesis	Non-inferiority	Non-inferiority	Non-inferiority
Primary endpoint	ACD, non-fatal MI, or all unplanned revascularization at 1 year	ACD, MI, any unplanned ischemia-driven revascularization, or cerebrovascular events at 1 year	ACD, non-fatal MI, stroke, unplanned ischemia-driven revascularization, or hospitalization for HF at 1 year
Key finding	Not revealed yet	Immediate CR (7.6%) was non-inferior to staged CR (9.4%) for the primary endpoint (HR 0.78, 95% CI 0.55-1.11, $P < .001$ for non-inferiority).	Primary endpoint occurred in 8.5% in immediate CR group as compared with 16.3% in staged CR group (risk ratio 0.52, 95% CI 0.38-0.72, $P < .001$ for non-inferiority).

Abbreviations: ACD, all-cause death; ACS, acute coronary syndrome; CI, confidence interval; CR, complete revascularization; FFR, fractional flow reserve; HF, heart failure; HR, hazard ratio; IRA, infarct-related artery; MI, myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

of the non-IRA. Two trials have compared FFR with angiography-guided PCI in non-IRA patients with STEMI and MVD. Our protocol for FFR guidance was similar to that used in previous trials. In the flow evaluation to guide revascularization in multivessel ST-elevation myocardial infarction (FLOWER-MI) trial, the FFR-guided strategy did not demonstrate any significant benefits compared to the angiography-guided strategy.¹⁶ However, this trial had several limitations, such as the high rate of staged PCI (96%), lower-than-expected event rate, and wide confidence interval, which necessitates caution when interpreting the study results. Conversely, the FFR-guided strategy was superior to the angiography-guided strategy in the FRAME-AMI trial.¹⁵

The European guideline for myocardial revascularization recommends the use of FFR for an intermediate stenosis of 40-90% diameter stenosis.¹⁹ The FFR criteria for lesions of more than 50% in the OPTION-STEMI trial is derived from the previous trials such as DANAMI3-PRIMULTI and COMPARE-ACUTE trials. Furthermore, the FLOWER-MI and FRAMI-AMI trial also used the 50% criteria. In the COMPLETE trial, the FFR was recommended for non-IRA lesions with 50%-69% diameter stenosis (although the most PCI was performed with angiography-guided). However, we acknowledge that a window for definition of an intermediate stenosis in the OPTION-STEMI trial is large. We will perform quantitative coronary angiography analysis in the core laboratory, and will perform additional analysis using quantitative coronary angiography and FFR data. No clear guidelines exist for the FFR evaluation of the non-IRA in STEMI patients. However, the use of FFR at the non-IRA in STEMI can reduce unnecessary coronary stenting. Furthermore, it is more cost-effective for AMI than the angiography-guided strategy.³⁰ We believe that routine FFR-guided

evaluation of the non-IRA will be an effective method for the management of the non-IRA in the OPTION-STEMI trial.

There have been concerns regarding the presence of plaque instability in the non-IRA because intravascular imaging was not performed routinely in this trial. In the post-hoc analysis of the FLOWER-MI trial, patients who received PCI showed favorable clinical outcomes compared to those who did not undergo PCI based on FFR results, suggesting that vulnerable plaques had a role in the progression of untreated lesions due to functional insignificance.³¹ Therefore, additional analysis using intravascular imaging will be required in the OPTION-STEMI trial.

Issues concerning immediate CR

Immediate CR is not a common clinical practice for the management of patients with STEMI and MVD. Although current guidelines and randomized clinical trials recommend that CR should be performed at the time of primary PCI or in a staged manner, many patients in these trials received staged CR rather than immediate CR, as per the operator's decision.^{6,19,16} The disadvantages of immediate CR include the high-risk of contrast-induced nephropathy, radiation exposure, complications during treating additional lesions, hemodynamic, and general clinical instability when treating additional lesions, risk of stent thrombosis, prothrombotic, and inflammatory milieu in the acute phase of STEMI, and overestimation of stenosis severity in the non-IRA due to coronary spasm.²⁸ It is possible that the operator may hesitate to perform immediate treatment of the non-IRA during off-hours due to the aforementioned factors and fatigue. However, immediate CR has an important advantage over staged CR. It can immediately treat secondary unstable lesions

which may have plaque instability.²⁸ In the BIOVASC and MULTISTARS AMI trials, the main difference between immediate and staged CR group was a higher incidence of non-fatal MI and repeat revascularization for untreated non-IRA lesions in the staged group. Interestingly, there were no significant differences in safety outcomes in the BIOVASC and MULTISTARS AMI trial between immediate and staged CR strategies. The crossover rate between groups was also low.^{10,11} Furthermore, there was no significant interaction effect between office hours and off hours on the primary endpoint in the prespecified subgroup analysis of the BIOVASC trial.¹⁰ However, further studies are needed to establish the efficacy and safety of the immediate CR strategy for patients with STEMI and MVD. The OPTION-STEMI trial will provide further insights into the clinical applications of immediate CR in patients with STEMI and MVD.

Summary

The optimal timing of CR in patients with STEMI and MVD remains uncertain. Although the results of recently published randomized clinical trials were introduced, current guidelines have not made recommendations in relation to the timing of CR. The OPTION-STEMI trial will compare immediate CR during primary PCI to in-hospital staged CR with routine FFR guidance for intermediate stenosis of the non-IRA in patients with STEMI and MVD.

Conflicts of Interest

The authors declare no disclosures or conflicts of interest.

CRedit authorship contribution statement

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.ahj.2024.03.017](https://doi.org/10.1016/j.ahj.2024.03.017).

References

1. Park DW, Clare RM, Schulte PJ, 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. Sorajja P, Gersh BJ, Cox DA, 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.
3. Byrne RA, Rossello X, Coughlan JJ, et al. 2023 ESC Guidelines for the management of acute coronary syndromes. *Eur Heart J* 2023;44:3720–826.
4. Lawton JS, Tamis-Holland JE, Bangalore S, et al. 2021 ACC/AHA/SCAI guideline for coronary artery revascularization: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2022;145:e18–114.

5. Wald DS, Morris JK, Wald NJ, et al. Randomized trial of preventive angioplasty in myocardial infarction. *N Engl J Med* 2013;369:1115–23.
6. Gershlick AH, Khan JN, Kelly DJ, 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.
7. Mehta SR, Wood DA, Storey RF, et al. Complete revascularization with multivessel PCI for myocardial infarction. *N Engl J Med* 2019;381:1411–21.
8. Engstrøm T, Kelbæk H, Helqvist S, et al. Complete revascularization 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.
9. Smits PC, Abdel-Wahab M, Neumann FJ, et al. Fractional flow reserve-guided multivessel angioplasty in myocardial infarction. *N Engl J Med* 2017;376:1234–44.
10. Diletti R, den Dekker WK, Bennett J, et al. Immediate versus staged complete revascularisation in patients presenting with acute coronary syndrome and multivessel coronary disease (BIOVASC): a prospective, open-label, non-inferiority, randomised trial. *Lancet* 2023;401:1172–82.
11. Stähli BE, Varbella F, Linke A, et al. Timing of complete revascularization with multivessel PCI for myocardial infarction. *N Engl J Med* 2023;389:1368–79.
12. van Nunen LX, Zimmermann FM, Tonino PA, et al. Fractional flow reserve versus angiography for guidance of PCI in patients with multivessel coronary artery disease (FAME): 5-year follow-up of a randomised controlled trial. *Lancet* 2015;386:1853–60.
13. Xaplanteris P, Fournier S, Pijls NHJ, et al. Five-year outcomes with PCI guided by fractional flow reserve. *N Engl J Med* 2018;379:250–9.
14. Thim T, van der Hoeven NW, Musto C, et al. Evaluation and management of nonculprit lesions in STEMI. *JACC Cardiovasc Interv* 2020;13:1145–54.
15. Lee JM, Kim HK, Park KH, et al. Fractional flow reserve versus angiography-guided strategy in acute myocardial infarction with multivessel disease: a randomized trial. *Eur Heart J* 2023;44:473–84.
16. Puymirat E, Cayla G, Simon T, et al. Multivessel PCI guided by FFR or angiography for myocardial infarction. *N Engl J Med* 2021;385:297–308.
17. Biscaglia S, Guiducci V, Escaned J, et al. Complete or culprit-only PCI in older patients with myocardial infarction. *N Engl J Med* 2023;389:889–98.
18. Toth GG, Johnson NP, Jeremias A, et al. Standardization of fractional flow reserve measurements. *J Am Coll Cardiol* 2016;68:742–53.
19. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J* 2019;40:87–165.
20. Ibanez B, James S, Agewall S, 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.
21. Gershlick AH, Banning AS, Parker E, et al. Long-term follow-up of complete versus lesion-only revascularization in STEMI and multivessel disease: the CvLPRIT trial. *J Am Coll Cardiol* 2019;74:3083–94.
22. Kim Y, Ahn Y, Cho MC, et al. Current status of acute myocardial infarction in Korea. *Korean J Intern Med* 2019;34:1–10.
23. Göteborg M, Christiansen EH, Gudmundsdottir U, et al. Instantaneous wave-free ratio versus fractional flow reserve to guide PCI. *N Engl J Med* 2017;376:1813–23.
24. Davies JE, Sen S, Dehbi HM, et al. Use of instantaneous wave-free ratio or fractional flow reserve in PCI. *N Engl J Med* 2017;376:1824–34.
25. Head SJ, Kaul S, Bogers AJ, Kappetein AP. Non-inferiority study design: lessons to be learned from cardiovascular trials. *Eur Heart J* 2012;33:1318–24.
26. Faro DC, Laudani C, Agnello FG, et al. Complete percutaneous coronary revascularization in acute coronary syndromes with multivessel coronary disease: a systematic review. *JACC Cardiovasc Interv* 2023;16:2347–64.
27. Wood DA, Cairns JA, Wang J, et al. Timing of staged nonculprit artery revascularization in patients with st-segment elevation myocardial infarction: COMPLETE trial. *J Am Coll Cardiol* 2019;74:2713–23.
28. Widimsky P, Jr Holmes DR. How to treat patients with ST-elevation acute myocardial infarction and multi-vessel disease? *Eur Heart J* 2011;32:396–403.
29. Pinilla-Echeverri N, Mehta SR, Wang J, et al. Nonculprit lesion plaque morphology in patients with ST-segment-elevation myocardial infarction: results from the COMPLETE trial optical coherence tomography substudies. *Circ Cardiovasc Interv* 2020;13:e008768.
30. Hong D, Lee SH, Lee J, et al. Cost-effectiveness of fractional flow reserve-guided treatment for acute myocardial infarction and multivessel disease: a prespecified analysis of the FRAME-AMI randomized clinical trial. *JAMA Netw Open* 2024;7:e2352427.
31. Denormandie P, Simon T, Cayla G, et al. Compared outcomes of ST-segment-elevation myocardial infarction patients with multivessel disease treated with primary percutaneous coronary intervention and preserved fractional flow reserve of nonculprit lesions treated conservatively and of those with low fractional flow reserve managed invasively: insights from the FLOWER-MI trial. *Circ Cardiovasc Interv* 2021;14:e011314.