ORIGINAL RESEARCH

Comparison of Long-Term Clinical Outcome Between Multivessel Percutaneous Coronary Intervention Versus Infarct-Related Artery–Only Revascularization for Patients With ST-Segment–Elevation Myocardial Infarction With Cardiogenic Shock

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Background—Data are limited regarding long-term outcomes in patients with ST-segment–elevation myocardial infarction and multivessel disease presenting with cardiogenic shock according to revascularization strategy. We sought to compare the 3-year clinical outcomes of patients with ST-segment–elevation myocardial infarction multivessel disease with cardiogenic shock and patients with multivessel percutaneous coronary intervention (PCI) and infarct-related artery (IRA)–only PCI.

Methods and Results—Of 13 104 patients from the nationwide, multicenter, prospective KAMIR-NIH (Korea Acute Myocardial Infarction Registry—National Institutes of Health) registry, we selected 659 patients with ST-segment–elevation myocardial infarction who had concomitant non-IRA stenosis and presented with cardiogenic shock. The primary outcome was all-cause death. Multivessel PCI was performed in 260 patients and IRA-only PCI in 399 patients. At 3 years, patients in the multivessel PCI group had a lower risk of all-cause death (adjusted hazard ratio, 0.65; 95% CI, 0.45–0.94 [*P*=0.024]), all-cause death or MI (adjusted hazard ratio, 0.59; 95% CI, 0.41–0.84 [*P*=0.004]), and non-IRA repeat revascularization (adjusted hazard ratio, 0.23; 95% CI, 0.10–0.50 [*P*<0.001]) than those in the IRA-only PCI group. The results were consistent after confounder adjustment by propensity score matching and inverse probability weighting analysis. Landmark analysis at 1 year demonstrated that the multivessel PCI group had a lower risk of recurrent MI and non-IRA repeat revascularization beyond 1 year (log-rank *P*=0.030 and *P*=0.017, respectively) than the IRA-only PCI group.

Conclusions—In patients with ST-segment–elevation myocardial infarction and cardiogenic shock, multivessel PCI was associated with a lower risk of all-cause death than IRA-only PCI at 3 years, suggesting potential benefit of non-IRA revascularization during the index hospitalization to improve long-term clinical outcomes. **(*J Am Heart Assoc*. 2019;8:e013870. DOI:10.1161/JAHA.119.013870e013870.)**

Key Words: cardiogenic shock • complete revascularization • multivessel disease • outcomes • percutaneous coronary intervention • ST-segment–elevation myocardial infarction

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Accompanying Appendix, Data S1, Table S1, Figures S1 and S2 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.013870

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Clinical Perspective

What Is New?

- In patients with ST-segment–elevation myocardial infarction multivessel disease complicated with cardiogenic shock, multivessel percutaneous coronary intervention (PCI) was associated with a lower risk of all-cause death, myocardial infarction, and non–infarct-related artery repeat revascularization at 3 years than infarct-related artery–only PCI.
- The 1-year landmark analysis showed that there was significantly lower risk of delayed adverse events in patients with multivessel PCI than in an infarct-related artery–only group for recurrent myocardial infarction and non–infarct-related artery repeat revascularization.
- In the multivessel PCI group, patients who underwent complete revascularization presented the most favorable prognosis at 3 years; however, patients who ended with incomplete revascularization showed similar risk of 3-year all-cause death and patient-oriented composite outcome with the infarct-related artery–only PCI group.

What Are the Clinical Implications?

- The results of this study support the long-term benefit of multivessel PCI in patients with ST-segment–elevation myocardial infarction with multivessel coronary artery disease who progressed to cardiogenic shock.
- In patients with ST-segment–elevation myocardial infarction with cardiogenic shock, achieving complete revascularization may be more important than the issue of timing of non–infarct-related artery PCI in terms of long-term outcomes.

About 5% to 10% of patients with ST-segment–elevation myocardial infarction (STEMI) present with cardiogenic shock and the mortality rate of this population is high.[1] Considering that up to 80% of patients with cardiogenic shock are known to have multivessel disease,[2] it is important to determine an appropriate revascularization strategy for concomitant non–infarct-related artery (IRA) lesions. European Society of Cardiology guidelines for STEMI have recommended consideration of non-IRA percutaneous coronary intervention (PCI) during the index procedure in patients with cardiogenic shock as a class IIa recommendation based on expert opinion.[3] However, the recent CULPRIT-SHOCK (Culprit Lesion Only PCI Versus Multivessel PCI in Cardiogenic Shock) trial, the only relevant randomized study on this issue, reported that immediate multivessel PCI increased the risk of 30-day all-cause death and new renal replacement therapy compared with IRA-only PCI.[4] This result contributed to the downgrade of routine revascularization of non-IRA lesions during primary PCI in patients with myocardial infarction (MI) and cardiogenic shock to class III in the most recent European guideline.[5]

However, our group previously reported that the risk of all-cause death at 1 year was significantly lower after multivessel PCI than IRA-only PCI using data from the KAMIR-NIH (Korea Acute Myocardial Infarction Registry—National Institutes of Health) registry.[6] Moreover, difference in mortality according to revascularization strategy disappeared and the risk of rehospitalization for heart failure and repeat revascularization was significantly lower with multivessel PCI than with culprit lesion–only PCI at 1-year follow-up of the CULPRIT-SHOCK trial.[7] These results emphasize the need for data on long-term clinical outcomes beyond 1 year to clarify appropriate revascularization strategy for non-IRA lesions in patients with STEMI complicated with cardiogenic shock. Therefore, we sought to compare clinical outcomes at 3 years after multivessel PCI versus IRA-only PCI in patients with STEMI who have cardiogenic shock and multivessel disease.

Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Population

We used data from the multicenter, prospective KAMIR-NIH registry, which is a dedicated registry that enrolled consecutive patients with acute MI from 20 nationwide tertiary centers eligible for primary PCI from November 2011 to December 2015, without applying any criteria for exclusion. Detailed study protocols have been published elsewhere.[6,8] The process of patient selection and the definition of STEMI, multivessel disease, and cardiogenic shock were presented in our previously published article[6] as well as in Data S1. In brief, we selected patients with STEMI who had multivessel disease who also presented with cardiogenic shock and underwent primary PCI. Presence of multivessel disease was defined as having additional ≥50% diameter stenosis in at least 1 major non-IRA or in the left main coronary artery. Cardiogenic shock was defined as systolic blood pressure <90 mm Hg for >30 minutes or the need for supportive management to maintain systolic blood pressure >90 mm Hg, clinical signs of pulmonary congestion, and evidence of impaired end-organ perfusion with at least 1 of the following: cool extremities, decreased urine output, increased lactic acid level, or altered mental status.[9] Complete revascularization was defined as revascularization for any lesion with a diameter stenosis ≥50% in any epicardial coronary artery with a reference vessel diameter ≥2.0 mm by visual estimation.

We excluded patients with a diagnosis of non–ST-segment–elevation myocardial infarction (NSTEMI) and those who arrived after >12 hours from onset of symptom, did not

present with cardiogenic shock, underwent thrombolysis before PCI, had single-vessel disease, underwent suboptimal or failed PCI for IRA, or were lost to follow-up before 1 year. A total of 659 patients were selected and classified into the multivessel PCI or IRA-only PCI group (Figure 1). We defined the multivessel PCI group as patients who underwent immediate non-IRA PCI during the primary PCI or staged non-IRA PCI within the index hospitalization.

The individual ethics committee at each participating center approved the protocol of the KAMIR-NIH registry. The present study was conducted according to the principles of the Declaration of Helsinki. All enrolled patients provided written informed consent. In cases of patients being unable to consent because of clinical status, a relative was informed and could provide consent on behalf of that patient.

Patient Treatment and Data Management

Patient treatment was performed according to current standard practice. The choice of treatment strategy; type, diameter, and length of stents; and use of medications, intravascular imaging devices, thrombus aspiration, or hemodynamic support devices were left to operator discretion. After PCI, all patients were recommended to take aspirin indefinitely plus clopidogrel or a potent P2Y12 inhibitor, such as prasugrel or ticagrelor, for at least 1 year.

Demographic features and cardiovascular risk factors were collected by patient interviews or review of medical records. During hospitalization, findings of coronary angiography and detailed procedural characteristics of PCI as well as information on discharge medications were collected. Attending physicians followed patients at 6, 12, 24, and 36 months after discharge. The data were completed by telephone interview if patients did not visit on their scheduled day of follow-up. Using a web-based case report form in the internet-based Clinical Research and Trial management system (iCReaT), independent clinical research coordinators collected all baseline data and clinical events up to 3 years of follow-up.

Study End Points

The primary outcome was all-cause death, and the secondary end point was all-cause death or recurrent MI at 3 years. Secondary end points also included cardiac death, non-IRA repeat revascularization, any repeat revascularization, definite

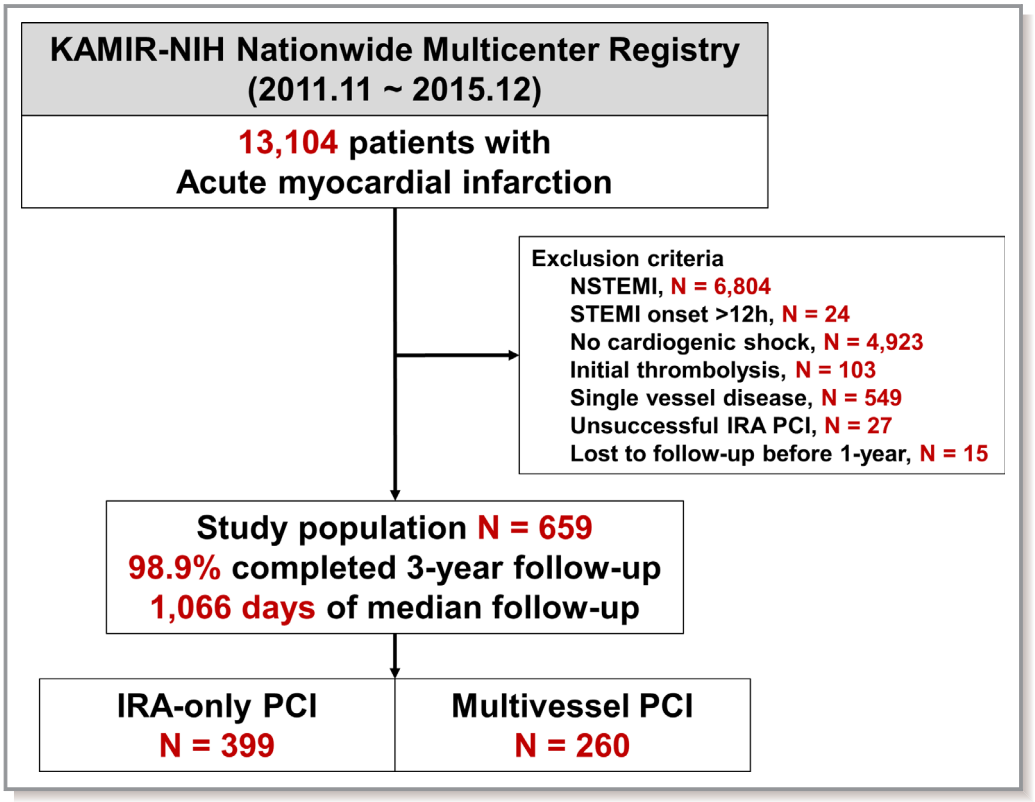

Figure 1. Study Flow. Study flow of patient selection and follow-up are presented. IRA indicates infarct-related artery; KAMIR-NIH, Korea Acute Myocardial Infarction Registry—National Institutes of Health; NSTEMI, non–ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment–elevation myocardial infarction.

or probable stent thrombosis, and patient-oriented composite outcome (a composite of all-cause death, any MI, or any repeat revascularization) at 3 years. All deaths were considered cardiac unless an undisputed noncardiac cause was present. Recurrent MI was defined as the recurrence of symptoms or the presence of ECG changes in association with a rise in cardiac biomarker levels above the upper limit of normal, and periprocedural MI was not included as a clinical outcome. Clinically driven revascularization that occurred after discharge from the index hospitalization was coded as a repeat revascularization event, and any planned revascularization was not considered as a clinical event. All end points were defined according to the definitions of the Academic Research Consortium.[10,11] All clinical events were evaluated by an independent event adjudicating committee. The definition of study end points and the process of event adjudication are described in the previous publication of KAMIR-NIH investigators.[8]

Statistical Analysis

Details of the statistical analysis are presented in Data S1. Categorical variables were presented as numbers and relative frequencies (percentages) and were compared using chi-square test. Continuous variables were expressed as mean±SD or median (quartile 1–quartile 3), according to whether they were normally distributed, and were compared using the independent sample *t* test or Mann–Whitney test, as appropriate. Cumulative incidence of events at 3 years was calculated based on Kaplan-Meier censoring estimates, and comparison of clinical outcomes between the multivessel PCI and IRA-only PCI groups was performed with the log-rank test. For the landmark analysis, patients at risk were reset to those who were free from events at the beginning of the landmark time point, which was 1 year after the index procedure in this analysis.

Sensitivity analyses were performed to adjust for confounding factors. First, a multivariable Cox regression model was used. Covariates included in the multivariable model were selected if they were significantly different between the 2 groups or had predictive values, which are listed in Data S1. The assumption of proportionality was assessed graphically by the log-minus-log plot, and Cox proportional hazard models for all clinical outcomes satisfied the proportional hazards assumption. For the landmark analysis, a Cox proportional hazard model with the assumption of piecewise proportionality according to the landmark time point was used.

Second, the propensity score–matched and inverse probability–weighted (IPW) Cox proportional hazard regression were performed. All available covariates were included in the logistic regression model to generate propensity scores, precisely following the recommendations of analysis using propensity score.[12] For the propensity score matching, a 1:1 matching process without replacements was performed by a greedy algorithm with a caliper width of 0.4 SDs, yielding 233 patients in the multivessel PCI group matched with 233 controls in the IRA-only PCI group. For the IPW adjustment, inverse of propensity score was adjusted in Cox proportional hazard regression model. Balance between the 2 groups after propensity score matching or IPW adjustment was assessed by percent standardized mean differences of all covariates. Percent standardized mean differences after propensity score matching or IPW adjustment were within ±10% across all matched covariates, demonstrating successful balance achievement between comparative groups (Table S1).

We established a multivariable Cox proportional hazard model to identify independent predictors of 3-year all-cause death and all-cause death or MI. C-statistics with 95% CIs were calculated to validate the discriminant function of the model. Comparison of the primary outcome according to the various exploratory subgroups was followed. In all analysis, the participating centers were included as random effects. All probability values were 2-sided and *P* values <0.05 were considered statistically significant.

Results

Baseline Characteristics

We analyzed the 3-year clinical outcomes of 659 patients with STEMI who had cardiogenic shock and concomitant non-IRA stenosis according to the PCI strategy (260 received multivessel PCI and 399 IRA-only PCI). Follow-up to 3 years was completed in 98.9% of the total patients with a median follow-up duration of 1066 days. Baseline clinical, lesion, and procedural profiles are described in Tables 1 and 2. One third of the patients with STEMI who had multivessel disease with cardiogenic shock experienced cardiac arrest at the visit, and the proportion of the left main artery as a culprit vessel was about 10%. Second-generation drug-eluting stents were implanted in 87.9% of patients, and 26.7% received at least 1 type of hemodynamic support including intra-aortic balloon pump or percutaneous cardiopulmonary support. Of patients in the multivessel PCI group, 157 patients (60.4%) underwent non-IRA PCI immediately after primary PCI during the index procedure, and 103 (39.6%) did staged non-IRA PCI during the index hospitalization. Complete revascularization was achieved in 171 patients (65.8%).

Comparison of 3-Year Outcomes According to Treatment Strategy

At 3 years, the risk of all-cause death was significantly lower in the multivessel PCI group than in the IRA-only PCI group (24.3% versus 37.7%) (adjusted hazard ratio, 0.65;

Table 1. Baseline Clinical Characteristics

	Total Population (N=659)	Multivessel PCI (n=260)	IRA-Only PCI (n=399)	*P* Value
Demographics				
Age, y	66.9±12.4	66.2±11.9	67.3±12.8	0.266
Age >65 y	384 (58.3)	150 (57.7)	234 (58.6)	0.808
Men	490 (74.4)	191 (73.5)	299 (74.9)	0.672
BMI, kg/m^2	23.5±3.2	23.6±3.1	23.4±3.2	0.396
Initial presentation				
Killip class 4	300 (45.6)	110 (42.5)	190 (47.6)	0.195
Cardiac arrest	236 (35.8)	85 (32.7)	151 (37.8)	0.178
Process of care index				
Symptom onset-to-balloon time, h	3.4 (2.1–7.2)	3.4 (2.1–8.5)	3.5 (2.0–6.8)	0.119
Door-to-balloon time, min	62.0 (48.0–82.0)	62.5 (47.0–84.0)	62.0 (49.0–81.0)	0.817
Cardiovascular risk factors				
Hypertension	354 (53.7)	136 (52.3)	218 (54.6)	0.558
DM	270 (41.0)	107 (41.2)	163 (40.9)	0.939
DM on insulin	20 (3.0)	5 (1.9)	15 (3.8)	0.179
Dyslipidemia	308 (46.7)	122 (46.9)	186 (46.6)	0.939
Chronic kidney disease	244 (37.0)	87 (33.5)	157 (39.3)	0.126
History of MI	53 (8.0)	17 (6.5)	36 (9.0)	0.252
Previous CHF admission	15 (2.3)	2 (0.8)	13 (3.3)	0.036
Previous history of CVA	57 (8.6)	20 (7.7)	37 (9.3)	0.480
Current smoking	250 (37.9)	105 (40.4)	145 (36.3)	0.296
LVEF, %	45.9±13.0	44.3±13.2	47.0±12.7	0.013
Peak cardiac enzyme levels				
CK-MB, ng/mL	202.4±247.5	216.3±319.1	193.4±186.6	0.295
Troponin I, ng/mL	85.9±133.1	95.4±158.6	79.2±111.8	0.189
Medications at discharge				
Aspirin	653 (99.1)	257 (98.8)	396 (99.2)	0.595
Clopidogrel	470 (71.3)	176 (67.7)	294 (73.7)	0.096
Prasugrel	60 (9.1)	32 (12.3)	28 (7.0)	0.021
Ticagrelor	119 (18.1)	48 (18.5)	71 (17.8)	0.828
ACEI or ARB	402 (61.0)	163 (62.7)	239 (59.9)	0.473
β-Blocker	430 (65.3)	182 (70.0)	248 (62.2)	0.039
Statin	498 (75.6)	204 (78.5)	294 (73.7)	0.163
Oral anticoagulant	19 (2.9)	11 (4.2)	8 (2.0)	0.095

Values are described as numbers (percentage), mean±SD, or median (quartile 1–quartile 3). Categorical variables were compared using chi-square test. Continuous variables were compared using independent sample *t* test or Mann–Whitney test, as appropriate. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CHF, congestive heart failure; CK-MB, creatine kinase-MB; CVA, cerebrovascular accident; DM, diabetes mellitus; IRA, infarct-related artery; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention.

95% CI, 0.45–0.94 [*P*=0.024]). All-cause death or MI and patient-oriented composite outcome also occurred less frequently with multivessel PCI than with IRA-only PCI (24.4% versus 40.3%) (adjusted hazard ratio, 0.59; 95% CI, 0.41–0.84 [*P*=0.004]) and 31.8% versus 50.8% (adjusted hazard ratio, 0.57; 95% CI, 0.44–0.73 [*P*<0.004]), respectively (Figure 2).

In addition to the composite end point, multivessel PCI was favored in most of the secondary end points such as cardiac death, recurrent MI, or any or non-IRA repeat

Table 2. Baseline Lesion- and Procedure-Related Profiles

	Total Population (N=659)	Multivessel PCI (n=260)	IRA-Only PCI (n=399)	*P* Value
Culprit lesion profiles				
Location				
Left main artery	62 (9.4)	39 (15.0)	23 (5.8)	0.001
LAD	238 (36.1)	91 (35.0)	147 (36.8)	
LCX	74 (11.2)	29 (11.2)	45 (11.3)	
RCA	285 (43.2)	101 (38.8)	184 (46.1)	
Type B2/C lesion*	595 (90.3)	233 (89.6)	362 (90.7)	0.638
Small vessel†	158 (25.5)	64 (25.5)	94 (25.5)	0.995
Long lesion‡	267 (43.1)	102 (40.6)	165 (44.7)	0.314
Overall lesion profiles				
Left main artery disease	87 (13.2)	47 (18.1)	40 (10.0)	0.003
3-Vessel disease	221 (33.5)	88 (33.8)	133 (33.3)	0.892
Procedural characteristics				
Transradial approach	96 (14.6)	28 (10.8)	68 (17.0)	0.055
Glycoprotein IIb/IIIa inhibitor use	154 (23.4)	64 (24.6)	90 (22.6)	0.542
Thrombus aspiration	206 (31.5)	73 (28.4)	133 (33.4)	0.177
IRA treatment				
Bare metal stent	38 (5.8)	13 (5.0)	25 (6.3)	0.190
First-generation DES	4 (0.6)	1 (0.4)	3 (0.8)	
Second-generation DES	579 (87.9)	237 (91.2)	342 (85.7)	
Plain balloon angioplasty	38 (5.8)	9 (3.5)	29 (7.3)	
Non-IRA treatment				
Bare metal stent	. . .	7 (2.7)	. . .	
First-generation DES	. . .	0 (0.0)	. . .	
Second-generation DES	. . .	219 (84.2)	. . .	
Plain balloon angioplasty	. . .	34 (13.1)	. . .	
Total number of implanted stents	1.55±0.87	2.24±0.83	1.10±0.54	<0.001
Pre-PCI TIMI flow in culprit lesion				
0	423 (64.2)	157 (60.4)	266 (66.7)	0.203
1	66 (10.0)	26 (10.0)	40 (10.0)	
2 or 3	170 (25.8)	77 (29.6)	93 (23.3)	
IVUS during PCI	120 (18.2)	52 (20.0)	68 (17.0)	0.336
OCT during PCI	12 (1.8)	2 (0.8)	10 (2.5)	0.103
Hemodynamic support device	176 (26.7)	72 (27.7)	104 (26.1)	0.644
IABP	155 (23.5)	65 (25.0)	90 (22.6)	0.470
PCPS/ECMO	52 (7.9)	22 (8.5)	30 (7.5)	0.661
Completeness of multivessel PCI				
Complete revascularization	. . .	171 (65.8)	. . .	. . .
Incomplete revascularization	. . .	89 (34.2)	. . .	. . .
Timing of non-IRA PCI				
Immediate PCI during index procedure	. . .	157 (60.4)	. . .	. . .
Staged PCI before discharge	. . .	103 (39.6)	. . .	. . .

Continued

Table 2. Continued

	Total Population (N=659)	Multivessel PCI (n=260)	IRA-Only PCI (n=399)	*P* Value
Periprocedural safety				
New renal replacement therapy during index hospitalization	22 (3.3)	9 (3.5)	13 (3.3)	0.887
New renal replacement therapy at 1 y	45 (6.8)	17 (6.5)	28 (7.0)	0.812

Values are described as numbers (percentages) or mean±SD. Categorical variables were compared using chi-square test. Continuous variables were compared using independent sample *t* test or Mann–Whitney test, as appropriate. DES indicates drug-eluting stent; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; IVUS, intravascular ultrasound; IRA, infarct-related artery; LAD, left anterior descending artery; LCX, left circumflex artery; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; PCPS, percutaneous cardiopulmonary support; RCA, right coronary artery; TIMI, Thrombolysis in Myocardial Infarction.

*Type B2 or C lesions according to American College of Cardiology/American Heart Association classification.

†Small vessel denotes lesion with reference diameter ≤2.75 mm.

‡Long lesion denotes lesion with length ≥28 mm.

revascularization; however, the risk of definite or probable stent thrombosis was not different between the 2 groups (Table 3). Consistent results were found in sensitivity analyses including multivariable Cox regression, propensity score matching, and IPW analysis. In the landmark analysis at 1 year, the risk of all-cause death tended to be lower with multivessel PCI than IRA-only PCI, yet statistical significance was not achieved. The risk of all-cause death or MI, recurrent MI, and non-IRA repeat revascularization beyond 1 year were significantly lower in the multivessel PCI group than in the IRA-only PCI group (Figure 3).

In analysis according to the completeness of revascularization after multivessel PCI, the incomplete multivessel PCI group showed a “catch-up” phenomenon in both all-cause death and all-cause death or MI, while those achieving complete revascularization had sustained benefit in all-cause death and all-cause death or MI without any catch-up phenomenon until 3 years (Figure S1). In an exploratory subgroup analysis, there was no significant interaction across various subgroups, and consistent trends favoring multivessel PCI in terms of all-cause death than IRA-only PCI were observed in all subgroups (Figure S2).

Independent Predictors of All-Cause Death and All-Cause Death or MI

A multivariable Cox proportional hazards model showed that multivessel PCI was a significant and negative independent predictor of all-cause death (hazard ratio, 0.555; 95% CI, 0.415–0.741 [*P*<0.001]) and all-cause death or MI (hazard ratio, 0.522; 95% CI, 0.392–0.694 [*P*<0.001]) at 3 years. Age, chronic kidney disease, diabetes mellitus, left main or left anterior descending artery as a culprit vessel, presence of left main disease, and 3-vessel disease were identified as independent predictors of all-cause death and all-cause death or MI (Table 4).

Discussion

The current study compared 3-year clinical outcomes after multivessel PCI versus IRA-only PCI among patients with STEMI multivessel disease complicated with cardiogenic shock. The main findings are as follows. First, the risk of all-cause death was significantly lower in the multivessel PCI group than in the IRA-only PCI group at 3 years, which was consistent in various sensitivity analyses with confounder adjustment. In addition, the risk of recurrent MI and non-IRA repeat revascularization was also significantly lower with multivessel PCI than with IRA-only PCI. Second, landmark analysis at 1 year showed that there was significantly lower risk of delayed adverse events in the multivessel PCI group than in the IRA-only PCI group in terms of recurrent MI and non-IRA repeat revascularization. Third, among patients in the multivessel PCI group, those undergoing complete revascularization had the most favorable prognosis at 3 years; however, those with incomplete revascularization showed late catch-up phenomenon and similar risk of all-cause death compared with the IRA-only PCI group. Fourth, an exploratory subgroup analysis showed consistent trends favoring multivessel PCI regarding all-cause death compared with IRA-only PCI.

Current Evidence and Need for Long-Term Data

In patients with STEMI who have cardiogenic shock, multivessel disease is common and is well known to have a detrimental impact on short- and long-term prognosis.[2] Results of the recently reported PRAMI (Preventive Angioplasty in Acute Myocardial Infarction), CvLPRIT (Complete Versus Lesion-Only Primary PCI Trial), DANAMI-3-PRIMULTI (Primary PCI in Patients With ST-elevation Myocardial Infarction and Multivessel Disease: Treatment of Culprit Lesion Only or Complete Revascularization), and Compare-Acute (Fractional Flow Reserve Guided Primary Multivessel Percutaneous Coronary Intervention to Improve Guideline Indexed Actual Standard of Care for Treatment of ST-elevation Myocardial

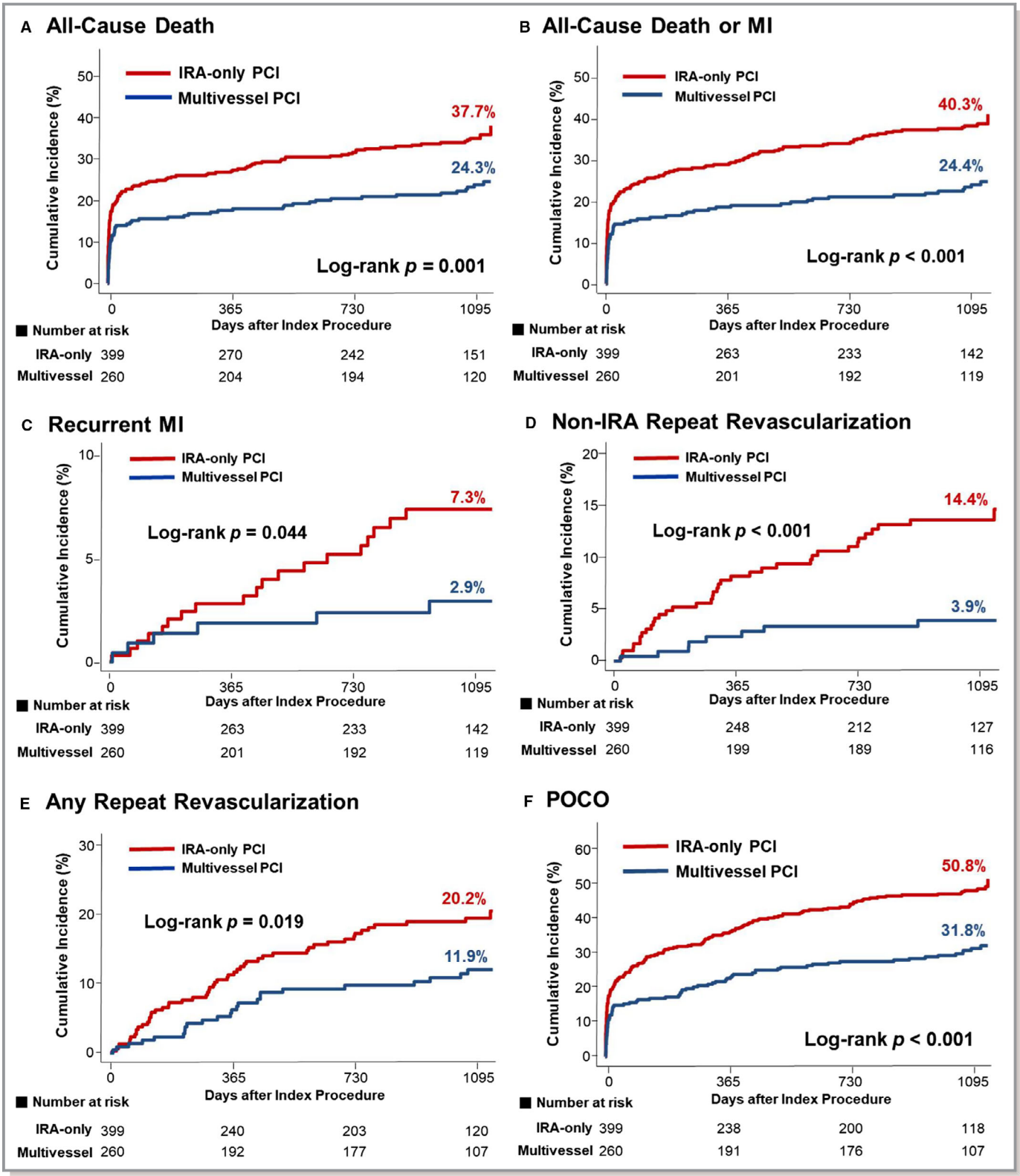

Figure 2. Cumulative incidence of clinical outcomes at 3 years. Kaplan-Meier curves with cumulative hazards of (**A**) all-cause death, (**B**) all-cause death or recurrent myocardial infarction (MI), (**C**) recurrent MI, (**D**) non–infarct-related artery (IRA) repeat revascularization, (**E**) any repeat revascularization, and (**F**) patient-oriented composite outcome (POCO), compared according to the percutaneous coronary intervention (PCI) strategy.

Table 3. Comparison of 3-Year Clinical Outcomes According to Treatment Strategy

	Multivessel PCI (n=260)	IRA-Only PCI (n=399)	Unadjusted		Multivariable-Adjusted		Propensity Score–Matched		IPW-Adjusted	
			HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
All-cause death	24.3% (67)	37.7% (155)	0.60 (0.45–0.80)	<0.001	0.65 (0.45–0.94)	0.024	0.66 (0.47–0.91)	0.011	0.63 (0.48–0.84)	0.002
Cardiac death	17.5% (50)	29.2% (126)	0.56 (0.40–0.77)	<0.001	0.65 (0.41–1.03)	0.069	0.61 (0.42–0.89)	0.010	0.55 (0.40–0.77)	0.001
Recurrent MI	2.9% (7)	7.3% (19)	0.47 (0.20–1.12)	0.090	0.50 (0.20–1.26)	0.142	0.46 (0.18–1.15)	0.095	0.42 (0.18–0.97)	0.042
Any repeat revascularization	11.9% (24)	20.2% (53)	0.57 (0.35–0.92)	0.020	0.52 (0.31–0.87)	0.013	0.44 (0.25–0.75)	0.003	0.53 (0.33–0.85)	0.008
Non-IRA repeat revascularization	3.9% (8)	14.4% (37)	0.27 (0.13–0.58)	0.001	0.23 (0.10–0.50)	<0.001	0.18 (0.07–0.43)	<0.001	0.24 (0.12–0.49)	<0.001
Definite or probable stent thrombosis	0.5% (1)	1.5% (4)	0.32 (0.04–2.88)	0.310	0.46 (0.03–6.78)	0.572	0.21 (0.02–1.89)	0.164	0.28 (0.03–2.36)	0.243
Readmission as a result of heart failure	4.8% (10)	7.1% (18)	0.72 (0.33–1.55)	0.396	0.79 (0.31–2.03)	0.619	2.73 (1.09–6.84)	0.032	1.09 (0.45–2.61)	0.852
All-cause death or MI	24.4% (68)	40.3% (165)	0.57 (0.43–0.75)	<0.001	0.59 (0.41–0.84)	0.004	0.60 (0.44–0.83)	0.002	0.59 (0.44–0.78)	<0.001
Patient-oriented composite outcome*	31.8% (86)	50.8% (203)	0.57 (0.44–0.73)	<0.001	0.55 (0.40–0.75)	<0.001	0.54 (0.40–0.71)	<0.001	0.56 (0.44–0.72)	<0.001

The cumulative incidence of clinical outcomes is presented as Kaplan-Meier estimates during a median follow-up of 1066.0 days. The numbers in parentheses in the columns of 2 groups indicate the number of patients with specific events. Multivariable Cox proportional hazard regression model, propensity score–matched cohort, and inverse probability of treatment weighting method were used to adjust for baseline differences between comparative groups. Covariates included in the multivariable model are type of treatment strategy, participating center, age older than 65 years, sex, Killip class at initial presentation, symptom onset-to-balloon time, door-to-balloon time, diabetes mellitus, dyslipidemia, chronic kidney disease, history of myocardial infarction (MI), history of cerebrovascular accident, current smoking, left ventricular dysfunction with ejection fraction <50%, left main artery or left anterior descending artery as a culprit vessel, left main artery disease, 3-vessel disease, small vessel ≤2.75 mm, long lesion ≥28 mm, and type B2 or C lesion according to the American College of Cardiology/American Heart Association classification. HR indicates hazard ratio; IPW, inverse probability weighting; IRA, infarct-related artery; PCI, percutaneous coronary intervention.

*Patient-oriented composite outcome was defined as a composite of all-cause death, recurrent MI, or any repeat revascularization.

Infarction in Patients With Multivessel Coronary Disease) trials demonstrated a significant benefit of multivessel PCI in hemodynamically stable patients with STEMI and multivessel disease.[13–16] However, these trials excluded patients with cardiogenic shock, and evidence from observational studies was also scarce. In the case of cardiogenic shock, controversy exists regarding the risks/benefits of multivessel PCI, such as concerns about possible procedure-related complications or contrast-induced nephropathy versus expectations for physiologic benefit through myocardial perfusion and recovery.[17,18]

In this context, the randomized CULPRIT-SHOCK trial was conducted, which reported that the risk of 30-day all-cause death or new renal replacement therapy was higher in the immediate multivessel PCI group than in the IRA-only PCI group.[4] Similarly, the BCCR (British Columbia Cardiac Registry) investigators recently reported that IRA-only PCI was associated with lower mortality in patients with acute MI who had cardiogenic shock, particularly in the STEMI subgroup.[19] Based primarily on the 30-day results from the CULPRIT-SHOCK trial, the latest update of the European guideline downgraded the immediate multivessel PCI for patients with acute MI multivessel disease with cardiogenic shock to a class III recommendation.[5] However, a subsequent 1-year report of the CULPRIT-SHOCK trial showed slightly different results from the 30-day results, and encouraged us to reconsider the possibility of long-term benefit of multivessel PCI in these patients. At 1-year follow-up, the difference in the primary end point (all-cause death and new renal replacement therapy) between the 2 groups lost its statistical significance, while the rate of rehospitalization for heart failure and repeat revascularization was significantly lower in the multivessel PCI group.[7] Moreover, previous 1-year results from the KAMIR-NIH registry presented a significantly lower risk of all-cause death and patient-oriented composite outcome in the multivessel PCI group compared with the IRA-only PCI group.[6] This result indirectly supports the possibility of long-term benefits of multivessel PCI to maximize left ventricular function recovery and to minimize the risk of future repeat revascularization. However, to date, there has been no evidence presenting long-term outcomes of patients with STEMI multivessel disease complicated with cardiogenic shock, according to treatment strategy. In this regard, we sought to analyze 3-year clinical outcomes of the KAMIR-NIH registry, a largescale data set that exclusively analyzed patients with STEMI who had cardiogenic shock and concurrent multivessel disease.

Long-Term Prognosis of Multivessel PCI in Patients With Multivessel Disease and Cardiogenic Shock

In the present study, the risk of all-cause death at 3 years after the index hospitalization was significantly lower in the

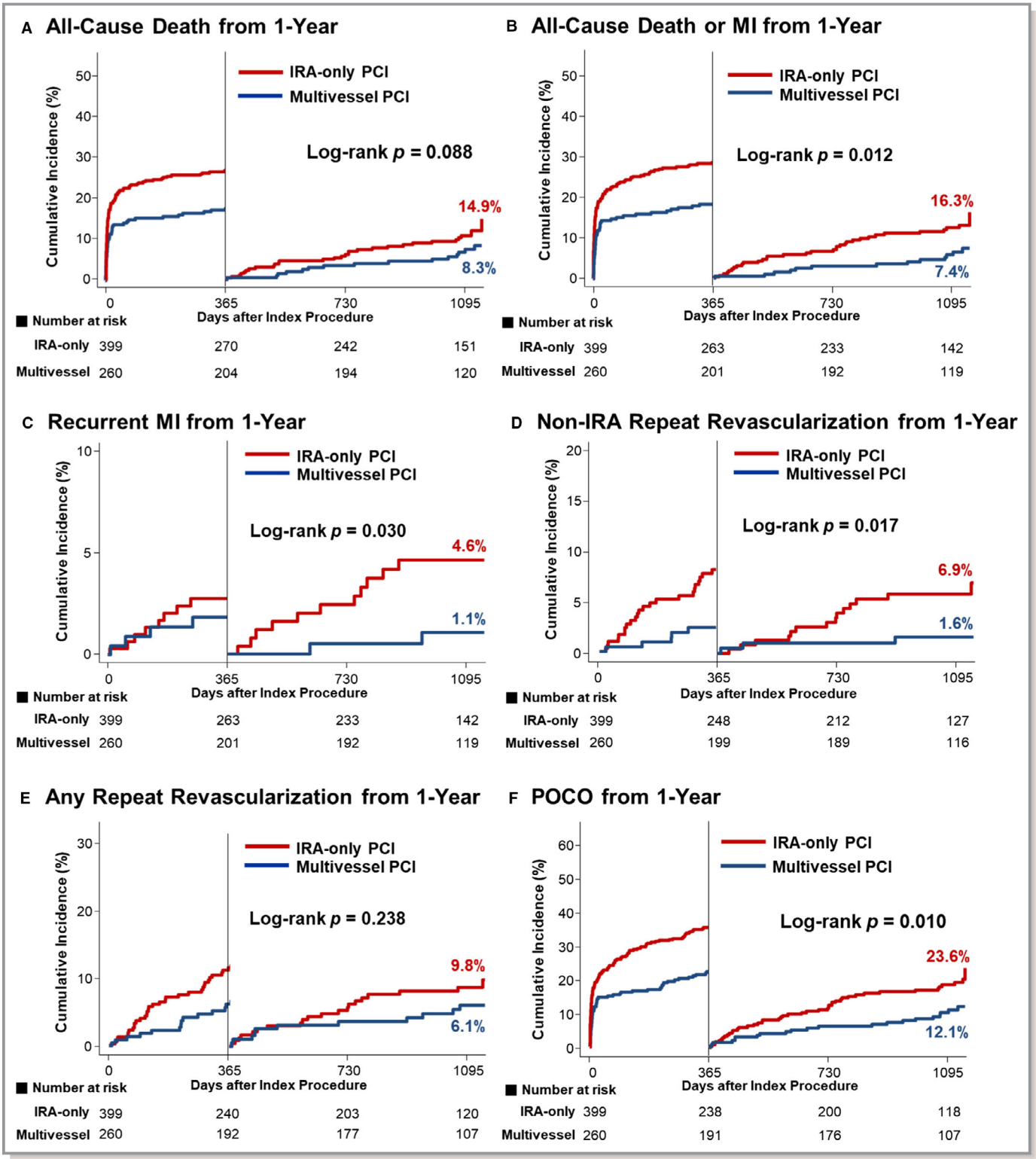

Figure 3. Landmark analysis of clinical outcomes from 1 year. Landmark analysis from 1 year of composite end points and individual outcomes, (**A**) all-cause death, (**B**) all-cause death or recurrent myocardial infarction (MI), (**C**) recurrent MI, (**D**) non–infarct-related artery (IRA) repeat revascularization, (**E**) any repeat revascularization, and (**F**) patient-oriented composite outcome (POCO). PCI indicates percutaneous coronary intervention.

multivessel PCI group than the IRA-only PCI group. Although it is difficult to explain the exact mechanism, revascularization for non-IRA might prevent recurrent MI and, in turn, reduce mortality. Landmark analysis at 1 year showed that the risk of recurrent MI was significantly lower in the multivessel PCI group than the IRA-only PCI group. In addition, when

Table 4. Independent Predictors for Clinical Outcomes at 3 Years

	HR	95% CI	*P* value
All-cause death			
Multivessel PCI (IRA-only PCI group as a reference)	0.56	0.42 to 0.74	<0.001
Age >65 y	3.02	2.17 to 4.21	<0.001
Left main or LAD as a culprit vessel	2.20	1.65 to 2.94	<0.001
Chronic kidney disease	1.85	1.41 to 2.43	<0.001
Presence of left main disease	1.69	1.16 to 2.45	0.006
3-Vessel disease	1.44	1.07 to 1.93	0.016
All-cause death or MI			
Multivessel PCI (IRA-only PCI group as a reference)	0.52	0.39 to 0.69	<0.001
Age >65 y	2.52	1.85 to 3.43	<0.001
Left main or LAD as a culprit vessel	2.19	1.65 to 2.90	<0.001
Chronic kidney disease	1.84	1.41 to 2.40	<0.001
Presence of left main disease	1.68	1.17 to 2.42	0.005
3-Vessel disease	1.41	1.06 to 1.88	0.019

Hazard ratios (HRs) and their 95% CIs were calculated by multivariable Cox regression analysis. The Harrell's C-index of the multivariable Cox proportional hazards model was 0.746 (95% CI, 0.713–0.780) for all-cause death and 0.728 (95% CI, 0.696–0.760) for all-cause death or myocardial infarction (MI). IRA indicates infarct-related artery; LAD, left anterior descending artery; PCI, percutaneous coronary intervention.

comparing 3-year clinical outcomes among IRA-only PCI, multivessel PCI with incomplete revascularization, and multivessel PCI with complete revascularization, patients achieving complete revascularization showed the most favorable prognosis, while those with incomplete revascularization had risk of all-cause death and all-cause death or MI similar to the IRA-only PCI group. These results are in line with the previous PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree: An Imaging Study in Patients With Unstable Atherosclerotic Lesions) trial, which showed more than half of clinical events in patients with acute coronary syndrome were related with non-IRA stenosis.[20] The above results imply that multivessel PCI might be associated with lower risk of future adverse events than IRA-only PCI. Furthermore, the above results might be intuitive, considering the results from previous trials that demonstrated consistent benefit of multivessel PCI compared with IRA-only PCI in hemodynamically stable patients with STEMI.[13–16]

It should be noted that there are some differences in study protocols and the definition of comparative groups, which may explain the discrepancies between the current results and those from the CULPRIT-SHOCK trial or the BCCR.[4,7,19] First, the CULPRIT-SHOCK trial and the BCCR registry analyzed both patients with STEMI and NSTEMI, not exclusively patients with STEMI. Second, in the CULPRT-SHOCK trial, the immediate multivessel PCI was mandated even for the chronic total occlusion in non-IRA, which accounted for 25% of the study population. Third, in the CULPRIT-SHOCK trial, staged non-IRA PCI was strongly recommended in the IRA-only PCI group, and ≈30% of the IRA-only PCI group was treated with the multivessel PCI strategy. Conversely, the multivessel PCI group used in the present study included both immediate or staged non-IRA PCI within the same admission period. All previous trials, except the CULPRIT-SHOCK trial, classified staged non-IRA PCI as multivessel PCI or complete revascularization.[13–16]

Study Limitations

There are some limitations to be discussed. First, we could not prove causality because of the observational nature of the registry data. Second, although confounding factors were thoroughly adjusted by various statistical methods, it was impossible to exclude the effects of unmeasured confounders, such as experience in patient management or procedure volume of participating centers. Third, the KAMIR-NIH registry was a clinical database that was not supplemented or linked by administrative data. Fourth, in consideration of possible uncontrolled bias in the decision of staged non-IRA revascularization, the prognosis of multivessel PCI by the timing of PCI could not be analyzed. However, it should be noted that timing of non-IRA PCI might be a clinical decision according to patient status, and therefore one uniform recommendation cannot be made considering diverse clinical situations. Fifth, outcomes such as recovery of left ventricular function, procedural complications, and long-term change of renal function were not included in the follow-up protocol. Finally, there was a lack of information regarding the type or dose of contrast agents and the procedure times.

Conclusions

In patients with STEMI multivessel disease complicated with cardiogenic shock, multivessel PCI was associated with a lower risk of all-cause death, recurrent MI, and non-IRA repeat revascularization at 3 years than IRA-only PCI. The multivessel PCI group showed a lower risk of recurrent MI and non-IRA repeat revascularization beyond 1 year compared with the IRA-only PCI group. The current results support that multivessel PCI in patients with STEMI who have multivessel disease and complicated with cardiogenic shock might be associated with lower risk of future adverse events than IRA-only PCI.

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Disclosures

None.

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Supplemental Material

Appendix

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Data S1.

Supplemental Methods

Population selection

Among a total of 13,104 patients enrolled in the KAMIR-NIH registry, we selected STEMI patients with multivessel disease who also presented with cardiogenic shock and underwent primary PCI. STEMI was defined as new ST-segment elevation in ≥2 contiguous leads measuring ≥0.1 mV, or a new left bundle branch block on 12-lead ECG, with a concomitant increase of at least one cardiac biochemical marker of necrosis. Presence of multivessel disease was defined as having additional ≥50% diameter stenosis in at least 1 major non-IRA or in the left main coronary artery as with previous trials. Cardiogenic shock was defined as systolic blood pressure <90 mmHg for >30 min or the need for supportive management to maintain systolic blood pressure >90 mmHg, clinical signs of pulmonary congestion, and evidence of impaired end organ perfusion with at least one of the following: cool extremities, decreased urine output, increased lactic acid level, or altered mental status. Patients were excluded from analysis if diagnosed as non-STEMI, arrived after >12 hours from symptom onset, not presenting with cardiogenic shock, underwent thrombolysis before PCI, had single vessel disease, underwent suboptimal or failed PCI for IRA, or were lost to follow-up before 1 year. As a result, 659 patients were selected for this analysis. Timeframe of the selected patients was the same as the original population. Among these, patients were classified according to treatment strategy: multivessel PCI or IRA-only PCI. Patients who underwent non-IRA PCI at the time of primary PCI or within index hospitalization were included in the multivessel PCI group.

Statistical analysis

Categorical variables were presented as numbers and relative frequencies (percentages) and were compared using the Chi-squared test. Continuous variables were expressed as mean ± standard deviation or median (Q1-Q3), according to whether they were normally distributed or not, and were compared using the independent sample t test or Mann-Whitney test, as appropriate. Cumulative event rates were calculated based on Kaplan-Meier censoring estimates, and comparison of clinical outcomes between multivessel PCI and IRA-

only PCI group was performed with the log-rank test. For the landmark analysis, patients at risk were reset to those who were free from events at the beginning of landmark timepoint, which was 1-year after index procedure in this analysis.

Since differences in baseline characteristics could significantly affect outcomes, sensitivity analyses were performed to adjust for confounders as much as possible. First, a multivariable Cox regression model was used. Covariates included in multivariable model were selected if they were significantly different between the 2 groups or had predictive values, which are listed as follows: type of treatment strategy (multivessel PCI or IRA-only PCI), age >65, sex, Killip class at initial presentation, symptom onset-to-balloon time, door-to-balloon time, diabetes mellitus, dyslipidemia, chronic kidney disease, previous history of MI, previous history of cerebrovascular accident, current smoking, left ventricular (LV) dysfunction with ejection fraction <50%, left main artery or LAD as a culprit vessel, left main artery disease, 3-vessel disease, small vessel ≤2.75 mm, long lesion ≥28 mm, and type B2 or C lesion according to the ACC/AHA classification. The assumption of proportionality was assessed graphically by the log-minus-log plot, and Cox proportional hazard models for all clinical outcomes satisfied the proportional hazards assumption. For the landmark analysis, a Cox proportional hazard model with the assumption of piecewise proportionality according to the landmark timepoint was used.

Second, the Cox proportional hazard regression in a propensity-score matched cohort and inverse probability weighted (IPW) Cox proportional hazard regression were performed. A multivariable logistic regression model was used to generate propensity-scores which indicate the probability that one would be treated by multivessel PCI strategy. All the available covariates were included to this model, precisely following the recommendations of analysis using propensity-score (1). For the propensity-score matching, a 1:1 matching process without replacements was performed by a greedy algorithm with a caliper width of 0.4 standard deviations, yielding 233 patients in the multivessel PCI group matched with 233 controls in the IRA-only PCI group. For the IPW adjustment, inverse of propensity score was adjusted proportional hazard regression model. Balance between the 2 groups after propensity-score matching or IPW adjustment was assessed by calculating percent standardized mean differences of covariates used in propensity-score generation. Percent standardized mean differences after propensity-score matching or IPW adjustment were

within ±10% across all matched covariates, demonstrating successful balance achievement between comparative groups (**Table S1**).

To identify independent predictors of all-cause death and POCO, we used multivariable Cox proportional hazard model. C-statistics with 95% confidence intervals (CI) were calculated to validate the discriminant function of the model. In addition, comparisons of the primary outcome between multivessel PCI and IRA-only PCI groups according to the exploratory subgroups of interest were followed, and the interaction between treatment effect and these covariates was assessed with Cox regression model. In all the analysis, the participating centers were included as random effects. All probability values were two-sided and p values <0.05 were considered statistically significant. The statistical packages SPSS version 22.0 (SPSS Inc., Chicago, IL, USA) and SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) were used for analyses.

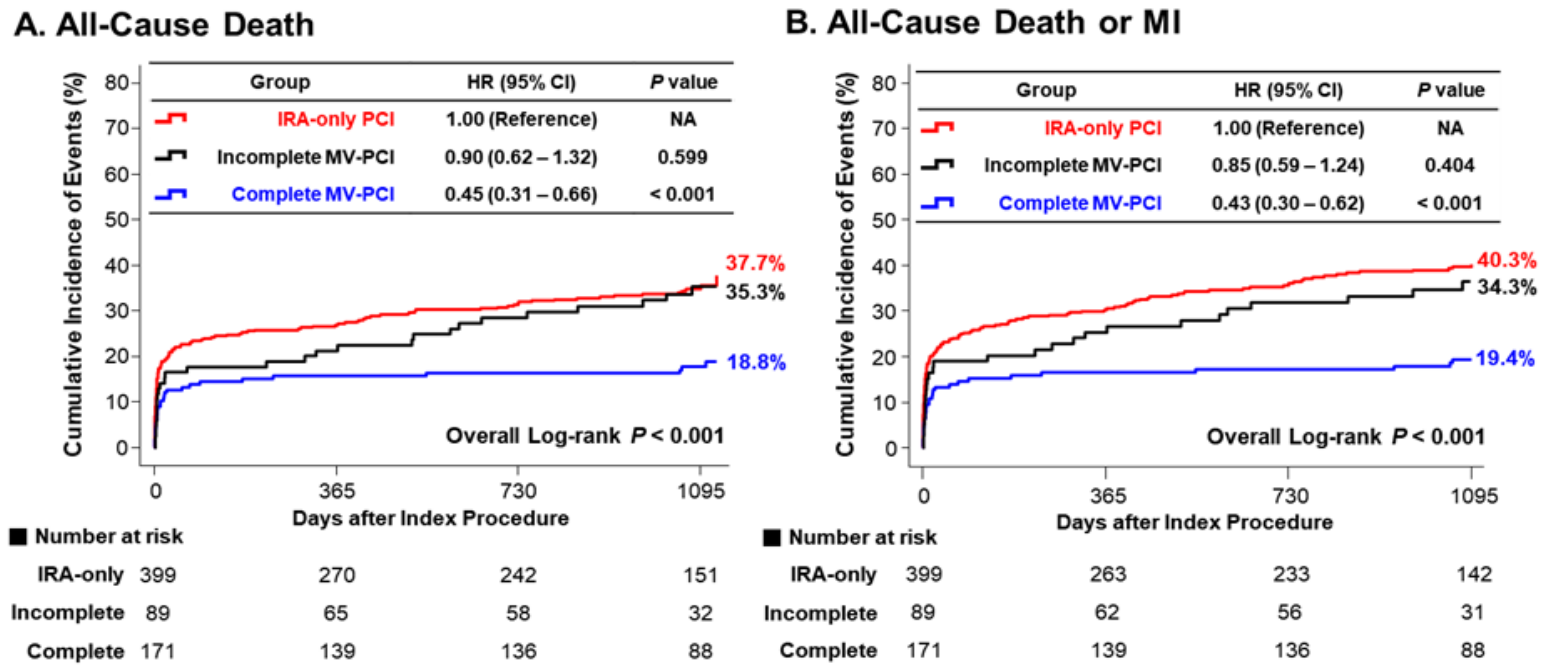
Table S1. Percent standardized differences of variables among unadjusted, propensity-score matched, and IPW-adjusted cohort, and baseline characteristics of propensity-score matched cohort.

	Percent standardized differences			Propensity-score matched cohort (N = 466)		
	Unadjusted (N = 659)	PS matched (N = 466)	IPW-adjusted (N=659)	Multivessel PCI (N = 233)	IRA-only PCI (N = 233)	*P value*
Age (years)	-8.9288	1.7979	-1.5351	66.5 ± 11.8	66.3 ± 13.0	0.846
Sex	3.3681	3.8772	-1.2862	27.5% (64)	25.8% (60)	0.675
Cardiac arrest	-10.7819	-3.6424	0.1004	32.2% (75)	33.9% (79)	0.694
Symptom onset-to-balloon time (hours)	12.7549	4.0707	0.9713	14.3 ± 35.3	12.9 ± 32.7	0.661
Killip class	-5.4537	0.0000	0.1931	-	-	0.961
I	-	-	-	23.6% (55)	24.0% (56)	-
II	-	-	-	3.9% (9)	4.3% (10)	-
III	-	-	-	29.6% (69)	27.5% (64)	-
IV	-	-	-	42.9% (100)	44.2% (103)	-
Hypertension	-4.6629	2.5732	-0.4298	53.2% (124)	51.9% (121)	0.781
Diabetes mellitus	0.6125	1.7403	0.3301	41.6% (97)	40.8% (95)	0.851
DM on insulin	-11.0528	3.5213	-1.0578	1.7% (4)	1.3% (3)	0.703
Dyslipidemia	0.6134	-4.2876	0.1603	46.8% (109)	48.9% (114)	0.643
Chronic kidney disease	-12.2382	-0.9090	-1.3950	33.0% (77)	33.5% (78)	0.922
Previous history of MI	-9.2694	-1.6696	-1.1171	6.9% (16)	7.3% (17)	0.857
Previous history of CVA	-5.6673	1.5841	-0.1977	8.2% (19)	7.7% (18)	0.864
Prior angina	-12.4364	0.0000	-0.8621	5.6% (13)	5.6% (13)	1.000
Current smoking	8.3098	-3.4924	0.6996	39.5% (92)	41.2% (96)	0.706
Location of culprit vessel	-22.1068	3.5738	0.3452	-	-	0.934
Left main artery	-	-	-	10.3% (24)	9.9% (23)	-
LAD	-	-	-	37.3% (87)	39.5% (92)	-

LCX	-	-	-	10.3% (24)	11.2% (26)	-
RCA	-	-	-	42.1% (98)	39.5% (92)	-
Left main artery disease	23.2879	3.8098	0.1727	13.7% (32)	12.4% (29)	0.680
3-vessel disease	1.0841	-0.8908	-0.2760	36.1% (84)	36.5% (85)	0.923
Type B2/C lesion	-3.7280	-2.8181	-1.3150	89.3% (208)	90.1% (210)	0.761
Small vessel	0.0544	-8.6645	-0.5402	25.3% (59)	29.2% (68)	0.349
Long lesion	-8.2381	0.8682	-0.4614	42.1% (98)	41.6% (97)	0.925
Pre-PCI TIMI flow grade	12.2701	-2.6205	1.6299	-	-	0.954
0	-	-	-	63.5% (148)	63.1% (147)	-
1	-	-	-	10.3% (24)	9.0% (21)	-
2	-	-	-	11.6% (27)	12.4% (29)	-
3	-	-	-	14.6% (34)	15.5% (36)	-

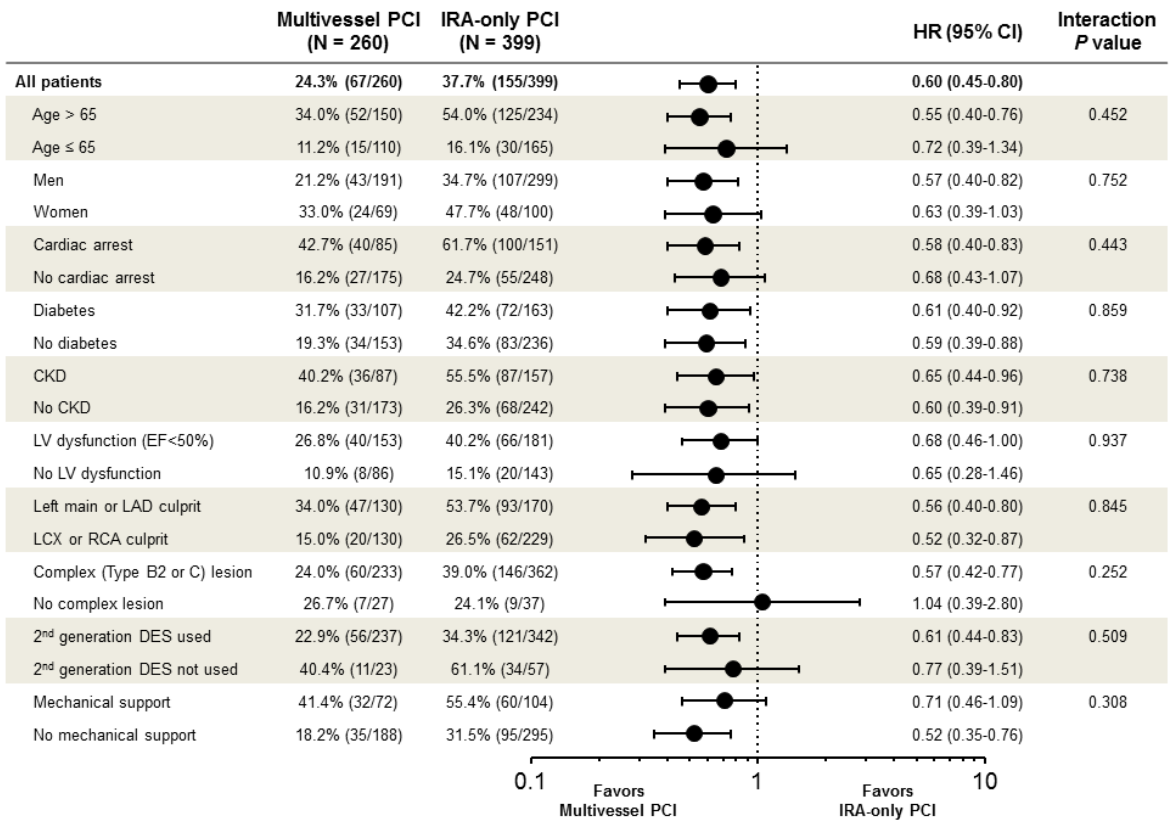
CVA, cerebrovascular accident; DM, diabetes mellitus; IPW, inverse probability weighting; MI, myocardial infarction; PCI, percutaneous coronary intervention; PS, propensity score; TIMI, The Thrombolysis In Myocardial Infarction.

Figure S1. Comparison of Outcomes at 3-Years According to Completeness of Multivessel PCI.



Kaplan-Meier curves and cumulative incidence of **(A)** all-cause death and **(B)** all-cause death or recurrent MI, compared among IRA-only PCI, incomplete and complete multivessel PCI are shown. IRA, infarct-related artery; KAMIR-NIH, the Korea Acute Myocardial Infarction Registry-National Institute of Health; NSTEMI, non ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

Figure S2. Exploratory Subgroup Analysis for All-Cause Death at 3-Years.



The results of exploratory subgroup analysis with the statistical analysis of interactions are presented. CKD, chronic kidney disease; DES, drug-eluting stents; EF, ejection fraction; LAD, left anterior descending artery; LCX, left circumflex artery; LV, left ventricular; RCA, right coronary artery; otherwise as in Figure 2.

Supplemental Reference:

1. Austin PC, Stuart EA. Moving toward best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. *Stat Med.* 2015;34:3661-79.