Journal of the American Heart Association

ORIGINAL RESEARCH

Culprit-Only Versus Immediate Multivessel Percutaneous Coronary Intervention in Patients With Acute Myocardial Infarction Complicating Advanced Cardiogenic Shock Requiring Venoarterial-Extracorporeal Membrane Oxygenation

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BACKGROUND: Despite the benefit of culprit-only percutaneous coronary intervention (PCI) in the CULPRIT-SHOCK (Culprit Lesion Only PCI Versus Multi-vessel PCI in Cardiogenic Shock) trial, the optimal revascularization strategy for refractory cardiogenic shock (CS) requiring mechanical circulatory support devices remains controversial. This study aimed to compare clinical outcomes between the culprit-only and immediate multivessel PCI strategies in patients with acute myocardial infarction complicated by CS who underwent venoarterial-extracorporeal membrane oxygenation before revascularization.

METHODS AND RESULTS: This study included patient-pooled data from the RESCUE (Retrospective and Prospective Observational Study to Investigate Clinical Outcomes and Efficacy of Left Ventricular Assist Devices for Korean Patients With Cardiogenic Shock) and SMC-ECMO (Samsung Medical Center–Extracorporeal Membrane Oxygenation) registries. A total of 315 patients with acute myocardial infarction with multivessel disease who underwent venoarterial-extracorporeal membrane oxygenation before revascularization attributable to refractory CS were included in this analysis. The study population was classified into culprit-only versus immediate multivessel PCI according to nonculprit lesion treatment strategies. The primary end point was 30-day mortality or renal-replacement therapy, and the key secondary end point was 12-month follow-up mortality. Among the study population, 175 (55.6%) underwent culprit-only PCI and 140 (44.4%) underwent immediate multivessel PCI. Compared with culprit-only PCI, immediate multivessel PCI was associated with significantly lower risks of 30-day mortality or renal-replacement therapy (68.0% versus 54.3%; *P*=0.018) and all-cause mortality during 12 months of follow-up (59.5% versus 47.5%; hazard ratio [HR], 0.689 [95% CI, 0.506–0.939]; *P*=0.018) in patients with acute myocardial infarction and CS who underwent venoarterial-extracorporeal membrane oxygenation before revascularization. These results were also consistent in the 99 pairs of propensity score–matched population (60.6% versus 43.6%; HR, 0.622 [95% CI, 0.420–0.922]; *P*=0.018).

CONCLUSIONS: Among patients with acute myocardial infarction with multivessel disease complicated by advanced CS requiring venoarterial-extracorporeal membrane oxygenation before revascularization, immediate multivessel PCI was associated

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This article was sent to Hani Jneid, MD, Associate Editor, for review by expert referees, editorial decision, and final disposition.

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.123.029792

For Sources of Funding and Disclosures, see page 11.

JAHA is available at: www.ahajournals.org/journal/jaha

with lower incidences of 30-day mortality or renal replacement therapy and 12-month follow-up mortality, compared with culprit-only PCI.

REGISTRATION INFORMATION: clinicaltrials.gov. Identifier: NCT02985008.

Key Words: acute myocardial infarction ■ cardiogenic shock ■ culprit ■ multivessel disease ■ percutaneous coronary intervention

CLINICAL PERSPECTIVE

What Is New?

- Although the CULPRIT-SHOCK (Culprit Lesion Only PCI Versus Multi-vessel PCI in Cardiogenic Shock) trial demonstrated that culprit-only percutaneous coronary intervention (PCI) was superior to immediate multivessel PCI in short-term mortality, the optimal treatment strategy for nonculprit lesions remains controversial in refractory cardiogenic shock (CS) requiring mechanical circulatory support before revascularization.
- Compared with the culprit-only PCI, the immediate multivessel PCI was associated with a reduced risk of short-term and 12-month follow-up mortality in patients with acute myocardial infarction with multivessel disease complicated by CS who underwent venoarterial-extracorporeal membrane oxygenation before revascularization.

What Are the Clinical Implications?

- The current findings imply that immediate nonculprit lesion revascularization during primary PCI might be considered in selective scenarios of CS, including in patients with a highly advanced form of CS requiring venoarterial-extracorporeal membrane oxygenation before revascularization.
- Future randomized trials are needed to identify the optimal treatment strategy in patients with acute myocardial infarction and CS who requiring mechanical circulatory support.

Nonstandard Abbreviations and Acronyms

CS	cardiogenic shock
CTO	chronic total occlusion
MCS	mechanical circulatory support
NCL	nonculprit lesion
RRT	renal-replacement therapy
SYNTAX	Synergy Between PCI With Taxus and Cardiac Surgery
TIMI	Thrombolysis in Myocardial Infarction
VA-ECMO	venoarterial-extracorporeal membrane oxygenation

Clinically significant nonculprit lesion (NCL) stenosis or occlusion in addition to an infarct-related artery can be found in 70% to 80% of patients with acute myocardial infarction (AMI) complicated by cardiogenic shock (CS) and is known to be associated with increased mortality compared with single-vessel disease.[1–3] The 2013 American College of Cardiology/American Heart Association and the 2017 European Society of Cardiology guidelines recommend percutaneous coronary intervention (PCI) of severe stenosis in NCLs during a primary procedure to improve overall myocardial perfusion and hemodynamic stability for patients with AMI and CS.[4] However, the CULPRIT-SHOCK (Culprit Lesion Only PCI Versus Multi-vessel PCI in Cardiogenic Shock) trial, which is the largest randomized trial in CS, demonstrated a 30-day risk of a composite of death or severe renal failure leading to renal-replacement therapy (RRT) was higher in the immediate multivessel PCI group than in the culprit-only PCI group.[5] Therefore, recently updated guidelines do not recommend routine NCL revascularization during primary PCI.[6,7]

Nevertheless, there are still unsolved issues surrounding the role of NCL revascularization for patients with CS, depending on the requirement of mechanical circulatory supports (MCSs) and the different stages of CS. In the CULPRIT-SHOCK trial, about one-quarter of patients, including 45 patients who underwent venoarterial-extracorporeal membrane oxygenation (VA-ECMO), received MCS devices, which are actively being used in real-world practice to rescue patients with CS. Moreover, at 1-year follow-up, a difference in mortality disappeared, and the incidence of rehospitalization for heart failure (HF) and risk of repeated revascularization was higher in a culprit-only PCI strategy.[8] Recently, data from the large US NCDR (National Cardiovascular Data Registry) showed that the multivessel PCI was associated with lower incidence of in-hospital all-cause mortality in patients with non–ST-segment–elevation myocardial infarction and CS requiring MCS.[9]

Therefore, we sought to compare the clinical outcomes between culprit-only and multivessel PCI as an index procedure in patients with AMI complicated by an advanced form of CS who underwent VA-ECMO.

METHODS

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Study Population and Data Collection

The patient-level pooled analysis included a total of 494 patients with AMI and CS who underwent VA-ECMO who were registered in the RESCUE (Retrospective and Prospective Observational Study to Investigate Clinical Outcomes and Efficacy of Left Ventricular Assist Devices for Korean Patients With Cardiogenic Shock) (NCT02985008) or SMC-ECMO (Samsung Medical Center–Extracorporeal Membrane Oxygenation) registries (Figure S1).[10] The criteria of CS in both registries included systolic blood pressure <90 mm Hg for 30 minutes or a state that required inotrope or vasopressor support to achieve a systolic blood pressure >90 mm Hg, and the presence of pulmonary congestion and signs of impaired organ perfusion (altered mental status, cold skin, urine output <0.5 mL/kg per hour for the previous 6 hours, or blood lactate >2.0 mmol/L). Patients with out-of-hospital cardiac arrest, those with other causes of shock, and those who refused active treatment were excluded from these registries. Among patients with AMI complicated by CS treated with primary PCI under VA-ECMO support (after exclusion of VA-ECMO after revascularization, n=121), 84.9% of patients (n=315) had a multivessel disease and were finally included in the current analysis (Figure S1).

Patient demographics, in-hospital management, laboratory data, procedural data, and outcome data were collected by independent clinical research coordinators in both RESCUE and SMC-ECMO registries. The follow-up data were prospectively collected at 1, 6, and 12 months using a web-based case record form in the RESCUE registry. In the SMC-ECMO registry, we also collected the follow-up data in the same manner. Additional information was obtained from medical records or telephone contact, if necessary. Institutional review board approval was obtained at each of the participating sites. The institutional review boards of the participating centers waived the requirement for informed consent in retrospectively enrolled patients, and informed consent was obtained before enrollment in all prospectively enrolled patients.

PCI Procedures and Angiographic Core Laboratory Analysis

Coronary interventions and best medical treatment were performed in accordance with standard guidelines at the time of each procedure.[11,12] The presence of NCL stenosis was defined as ≥50% diameter stenosis in at least 1 major non–infarct-related artery.[13] The choice of revascularization strategy was at the operator's discretion. All patients who were not taking aspirin or a P2Y12 inhibitor received a loading dose of aspirin (300 mg) or a P2Y12 inhibitor (clopidogrel, 300–600 mg; ticagrelor, 180 mg; or prasugrel, 60 mg). Anticoagulation during PCI was performed using low-molecular-weight heparin or unfractionated heparin to achieve an activated clotting time of 250 to 300 s.

All angiograms were collected and analyzed at a core laboratory (Heart Vascular Stroke Institute, Samsung Medical Center, Seoul, Republic of Korea). The culprit and nonculprit lesion locations, presence of nonculprit chronic total occlusion (CTO) lesion, and percentage diameter stenosis with TIMI (Thrombolysis in Myocardial Infarction) flow grades in both culprit and nonculprit vessels were assessed by 3 experienced cardiovascular technicians using a blinded approach. The Synergy Between PCI With Taxus and Cardiac Surgery (SYNTAX) score was calculated to assess the atherosclerotic burden in epicardial coronary arteries, using an online SYNTAX score calculator. The residual SYNTAX score was based on the last frames of final angiography during the index hospitalization to analyze the residual ischemic burden after PCI.

VA-ECMO Management

Mechanical hemodynamic support using VA-ECMO was considered on the basis of current guideline recommendations.[11,12,14–16] Management during VA-ECMO support was also based on the Extracorporeal Life Support Organization guideline.[17] Peripheral VA-ECMO cannulation was the most frequently applied for access and performed via the common femoral artery and vein just below the inguinal ligament and above their respective bifurcations. A 15F to 17F arterial cannula and a 21F to 28F venous cannula were used to supply sufficient flow depending on the needs of the patient. Continuous unfractionated heparin was infused intravenously to maintain an activated clotting time between 150 and 180 s or between 180 and 220 s, according to the protocol of each hospital if there are no contraindications. When performing the distal perfusion catheter insertion, a fluoroscopy- or ultrasound-guided approach was used. Left ventricular unloading was selectively performed by transseptal left atrial cannulation via the femoral vein, pulmonary artery cannulation via the jugular vein, insertion of intra-aortic balloon pump, or conversion of central ECMO (surgically) according to the clinicians' decision. VA-ECMO weaning was considered when patients were hemodynamically stable without any vasopressors or with a low level of pharmacological support (norepinephrine, ≤0.05 mg/kg per minute; and/or dobutamine, ≤5 mg/kg per minute) and had a mean arterial pressure ≥65 mm Hg, lactate <2 mmoL/L, and central vein pressure ≤15 mm Hg.

Definitions and Outcomes

The primary end point of the current study was 30-day mortality or RRT, and the key secondary end point was 12-month follow-up all-cause mortality. Other secondary end points included 30-day mortality, 30-day cardiac mortality, 30-day RRT, poor neurologic outcome at discharge, successful VA-ECMO weaning, 12-month follow-up recurrent myocardial infarction, HF rehospitalization, repeated revascularization, and a composite of all-cause mortality, myocardial infarction, or HF rehospitalization.

All deaths were considered cardiac death unless a definite noncardiac cause was established. Poor neurologic outcome was defined as Cerebral Performance Category ≥3.[18] Successful weaning of VA-ECMO was defined as successful removal of VA-ECMO and not requiring further mechanical support because of recurring CS over the following 48 hours.

Statistical Analysis

Categorical variables are presented as numbers and relative frequencies, and their group differences were compared using the χ^2 test. Continuous variables were compared between groups using the Welch *t*-test and are presented as means±SDs or medians with interquartile ranges. Cumulative incidences of adverse events during follow-up are presented as a Kaplan-Meier estimate, and the significance level was assessed with a log-rank test. Cox proportional hazard regression models were used to calculate hazard ratios (HRs) and 95% CIs, and the proportional hazards assumptions of the HRs in the Cox proportional hazards models were graphically inspected in the "log minus log" plot and were also tested by Schoenfeld residuals. In multivariable models, clinically relevant covariates were selected as candidate variables. A propensity score matching analysis was also performed to reduce selection bias and potential confounding factors. For propensity score matching analysis, a full nonparsimonious model was developed to include all variables, which were clinically relevant, listed in Table S1. Patients in the 2 groups were matched 1:1 on the logit of the propensity score with a caliper width of 0.1 of the SD of the logit of the propensity score, and 99 pairs were finally matched (Figure S2). The covariate balance after propensity score matching was assessed by calculating percentage standardized mean differences. The absolute standardized mean difference after propensity score matching was within ±10% across all matched covariates, demonstrating that a successful balance was achieved between comparative groups. Stratified Cox proportional hazard models with robust variance were used to compare the outcomes of the matched groups.

All probability values were 2 tailed, and $P<0.05$ was considered statistically significant. Statistical analyses were performed using R Statistical Software (version 4.0.2; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline Characteristics

Among the total study population, 175 patients (55.6%) received culprit-only PCI and 140 (44.4%) received immediate multivessel PCI. The mean age of the study population was 65.3±11.5 years, 247 patients (78.4%) were men, and 218 patients (69.2%) received periprocedural cardiopulmonary resuscitation because of cardiac arrest. The mean systolic blood pressure and lactic acid level were 51.6±37.7 mm Hg and 7.6±4.7 mmol/L, respectively. There were no significant differences in all baseline clinical demographics, cardiovascular risk factors, clinical presentation, severity of shock, and in-hospital and VA-ECMO management between culprit-only and immediate multivessel PCI groups (Table 1). In angiographic characteristics, the culprit lesion location and pre- and post-PCI culprit lesion TIMI flow grade did not differ significantly between the 2 groups. However, compared with patients who underwent culprit-only PCI, those with immediate multivessel PCI had a higher prevalence of 3-vessel disease, a higher number of lesions and the use of stents, a higher pre-PCI SYNTAX score, and a greater NCL percentage diameter stenosis (Table 2). In contrast, the residual SYNTAX score was significantly lower in the immediate multivessel PCI group than in the culprit-only PCI group. The overall contrast volume of index PCI was significantly higher in the immediate multivessel PCI group, but staged PCI was more frequently performed in the culprit-only PCI group (Table 2).

In-Hospital and 12-Month Follow-Up Clinical Outcomes

Among the 315 patients with AMI complicated by CS who underwent VA-ECMO before revascularization, an immediate multivessel PCI at the index procedure was associated with significantly lower risks of 30-day mortality or RRT compared with the culprit-only PCI (culprit-only versus immediate multivessel PCI, 68.0% versus 54.3%; $P=0.018$) (Figure 1). Similarly, the rates of 30-day mortality (51.4% versus 39.3%; $P=0.042$), cardiac mortality (47.4% versus 35.7%; $P=0.048$), and poor neurologic outcomes defined by Cerebral Performance Category 3 to 5 at discharge (62.9% versus 49.3%; $P=0.021$) were significantly lower in the immediate multivessel PCI group than in the culprit-only PCI group. There was no significant difference in

Table 1. Baseline Clinical Characteristics, Shock Severity, and In-Hospital and ECMO Management

Variable	Total (n=315)	Culprit-only PCI (n=175)	Multivessel PCI (n=140)	*P* value
Demographics				
Age, y	65.3±11.5	65.4±11.5	65.3±11.6	0.948
Male sex	247 (78.4)	138 (78.9)	109 (77.9)	0.939
Body mass index, kg/m^2	24.4±3.4	24.3±3.3	24.6±3.5	0.433
Hypertension	174 (55.2)	92 (52.6)	82 (58.6)	0.342
Diabetes	152 (48.3)	83 (47.4)	69 (49.3)	0.830
Dyslipidemia	65 (20.6)	35 (20.0)	30 (21.4)	0.864
Chronic kidney disease	31 (9.8)	15 (8.6)	16 (11.4)	0.512
Current smoking	95 (30.2)	52 (29.7)	43 (30.7)	0.945
Previous myocardial infarction	67 (21.3)	33 (18.9)	34 (24.3)	0.302
Peripheral artery disease	13 (4.1)	9 (5.1)	4 (2.9)	0.466
Previous history of stroke	28 (8.9)	17 (9.7)	11 (7.9)	0.707
Clinical presentation and severity at shock				
Initial presentation				
NSTEMI	102 (32.4)	52 (29.7)	50 (35.7)	0.313
STEMI	213 (67.6)	123 (70.3)	90 (64.3)	
LVEF, %	25.0 (17.6–35.0)	25.0 (15.0–35.0)	27.5 (19.1–35.0)	0.373
Systolic blood pressure, mm Hg	62.0 (0–79.0)	64.0 (0–78.0)	62.0 (0–81.5)	0.293
Diastolic blood pressure, mm Hg	40.0 (0–52.0)	40.0 (0–51.0)	43.0 (0–53.5)	0.105
Heart rate, beats/min	67.0 (0–99.0)	62.5 (0–98.0)	72 (30.0–102.0)	0.125
Hemoglobin, g/dL	12.7 (10.9–14.7)	12.6 (11.0–14.7)	13.0 (10.4–14.6)	0.307
Creatinine, mg/dL	1.29 (1.00–1.70)	1.30 (1.02–1.70)	1.25 (0.98–1.71)	0.548
Glucose, mg/dL	218.0 (154.0–310.0)	230.0 (154.0–323.0)	206.0 (153.0–295.0)	0.440
Lactic acid, mmol/L	6.8 (3.7–10.5)	7.6 (4.3–11.0)	6.1 (3.1–10.1)	0.138
Peak troponin I, ng/mL	60.4 (9.2–380.6)	50.0 (8.1–386.9)	65.7 (9.6–358.8)	0.629
IABP-SHOCK 2 score	2.0 (1.0–4.0)	2.0 (1.0–4.0)	2.0 (1.0–3.0)	0.131
Undergoing CPR	218 (69.2)	128 (73.1)	90 (64.3)	0.117
Arrest rhythm				
VT or VF	96/218 (44.0)	56/128 (43.8)	40/90 (44.4)	0.999
PEA or asystole	122/218 (56.0)	72/128 (56.2)	50/90 (55.6)	
In-hospital management				
Use of vasoactive drug	302 (95.9)	167 (95.4)	135 (96.4)	0.874
Mechanical ventilation	275 (87.3)	153 (87.4)	122 (87.1)	0.999
Requiring RRT	114 (36.2)	65 (37.1)	49 (35.0)	0.783
Left ventricular unloading	63 (20.0)	38 (21.7)	25 (17.9)	0.479
Transseptal left atrial cannulation	20 (6.3)	11 (6.3)	9 (6.4)	0.999
Combined IABP insertion	44 (14.0)	27 (15.4)	17 (12.1)	0.501
ICU stays, d (survived patients only)	12.0 (6.0–19.0)	11.0 (6.0–17.5)	12.5 (7.0–21.0)	0.487
Hospital stays, d (survived patients only)	22.5 (14.0–50.0)	23.5 (15.0–48.0)	21.0 (12.0–51.0)	0.738
ECMO management				
Fluoroscopy guidance	235 (74.6)	130 (74.3)	105 (75.0)	0.988
Shock to ECMO time, min	56.0 (30.0–110.0)	57.0 (33.0–120.0)	53.0 (28.0–104.0)	0.591
Distal perfusion	115 (36.5)	58 (33.1)	57 (40.7)	0.204
Initial pump flow, L/min	3.1 (2.5–3.6)	3.1 (2.5–3.6)	3.1 (2.5–3.7)	0.827
ECMO maintenance duration, d	4.0 (2.0–6.0)	4.0 (2.0–7.0)	4.0 (2.0–6.0)	0.812
Successful ECMO weaning	191 (64.8)	99 (60.0)	92 (70.8)	0.072

Values are mean±SD, median (interquartile range), number (percentage), or number/total (percentage).

CPR indicates cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; IABP-SHOCK, IABP in cardiogenic shock; ICU, intensive care unit; LVEF, left ventricular ejection fraction; NSTEMI, non–ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; PEA, pulseless electrical activity; RRT, renal-replacement therapy; STEMI, ST-segment–elevation myocardial infarction; VF, ventricular fibrillation; and VT, ventricular tachycardia.

Table 2. Baseline Angiographic and Procedural Characteristics

Variable	Total (n=315)	Culprit-only PCI (n=175)	Multivessel PCI (n=140)	*P* value
Angiographic findings				
Culprit lesion location				
LM	109 (34.6)	59 (33.7)	50 (35.7)	0.349
LAD	102 (32.4)	53 (30.3)	49 (35.0)	
LCX	33 (10.5)	17 (9.7)	16 (11.4)	
RCA	71 (22.5)	46 (26.3)	25 (17.9)	
Culprit lesion TIMI flow grade, pre-PCI				
0	154 (48.9)	86 (49.1)	68 (48.6)	0.738
1	38 (12.1)	24 (13.7)	14 (10.0)	
2	68 (21.6)	36 (20.6)	32 (22.9)	
3	55 (17.5)	29 (16.6)	26 (18.6)	
Culprit lesion TIMI flow grade, post-PCI				
0	4 (1.3)	3 (1.7)	1 (0.7)	0.279
1	7 (2.2)	6 (3.4)	1 (0.7)	
2	31 (9.8)	15 (8.6)	16 (11.4)	
3	273 (86.7)	151 (86.3)	122 (87.1)	
Nonculprit lesion location (per-vessel)	n=453	n=246	n=207	
LM	8 (2.5)	2 (1.1)	6 (4.3)	0.161
LAD	121 (38.4)	71 (40.6)	50 (35.7)	0.445
LCX	192 (61.0)	101 (57.7)	91 (65.0)	0.230
RCA	132 (41.9)	72 (41.1)	60 (42.9)	0.848
Vessel disease				
2-Vessel disease	158 (50.2)	97 (55.4)	61 (43.6)	0.048
3-Vessel disease	157 (49.8)	78 (44.6)	79 (56.4)	
SYNTAX score, pre-PCI	29.9±11.2	27.8±11.0	32.4±11.0	<0.001
SYNTAX score, post-PCI	9.3±9.6	11.2±10.1	7.0±8.4	<0.001
Δ SYNTAX score	20.6±11.1	16.7±9.9	25.4±10.6	<0.001
No. of lesions	2.8±1.2	2.6±1.1	3.0±1.2	0.002
Nonculprit CTO lesion	103 (32.7)	65 (37.1)	38 (27.1)	0.079
Calcified lesion	106 (33.7)	50 (28.6)	56 (40.0)	0.044
Nonculprit vessel diameter stenosis, %	87.4±15.1	84.3±17.1	91.2±11.2	<0.001
Procedural characteristics				
Access site				
Femoral artery	276 (87.6)	151 (86.3)	125 (89.3)	0.528
Radial artery	39 (12.4)	24 (13.7)	15 (10.7)	
Contrast volume, mL	166.2±77.7	136.9±55.9	200.6±85.8	<0.001
Implanted device				
Drug-eluting stent	245 (77.8)	131 (74.9)	114 (81.4)	0.267
Balloon angioplasty or thrombectomy only	50 (15.9)	33 (18.9)	17 (12.1)	
Others	20 (6.3)	11 (6.3)	9 (6.4)	
Shock-to-balloon time, min	87.0 (53.0–138.0)	87.0 (57.0–135.0)	85.0 (49.0–144.0)	0.625
ECMO-to-balloon time, min	34.5 (18.0–67.0)	36.0 (19.5–67.5)	33.0 (18.0–63.0)	0.845
Treated lesion No.	1.7±0.9	1.2±0.5	2.3±0.9	<0.001
No. of stents	1.4±1.1	1.0±0.7	2.0±1.2	<0.001
Thrombus aspiration	115 (36.5)	58 (33.1)	57 (40.7)	0.204
Glycoprotein IIb/IIIa inhibitor	24 (7.6)	11 (6.3)	13 (9.3)	0.433

(*Continued*)

Table 2. Continued

Variable	Total (n=315)	Culprit-only PCI (n=175)	Multivessel PCI (n=140)	*P* value
CTO revascularization at index PCI				
Not attempted	86/103 (83.5)	65/65 (100)	21/38 (55.3)	<0.001
Successful revascularization	12/103 (11.7)	0/65 (0)	12/38 (31.6)	
Failed revascularization	5/103 (4.9)	0/65 (0)	5/38 (13.2)	
Performed staged PCI	21 (6.7)	18 (10.3)	3 (2.1)	0.008
Timing of staged PCI, d	2.0 (1.0–4.0)	3.5 (2.0–6.0)	0.0 (0.0–1.0)	0.037

Values are mean±SD, median (interquartile range), number (percentage), or number/total (percentage). CTO indicates chronic total occlusion; ECMO, extracorporeal membrane oxygenation; LAD, left anterior descending artery; LCX, left circumflex artery; LM, left main coronary artery; PCI, percutaneous coronary intervention; RCA, right coronary artery; SYNTAX, Synergy Between PCI With Taxus and Cardiac Surgery; and TIMI, Thrombolysis in Myocardial Infarction.

the risk of 30-day RRT (37.1% versus 35.0%; *P*=0.783) between the 2 groups (Figure 1). Short-term outcome between the 2 groups showed similar trends in propensity score–matched population (Figure S3). At 12 months of follow-up, patients who received immediate multivessel PCI had significantly lower risks of all-cause mortality (59.5% versus 47.5%; HR, 0.689 [95% CI, 0.506–0.939]; *P*=0.018) and a composite of all-cause mortality, myocardial infarction, and HF rehospitalization (HR, 0.741 [95% CI, 0.575–0.955]; *P*=0.021) than those who received culprit lesion only PCI (Figure 2A and Table 3). The multivariable analysis showed consistent results after the adjustment of various clinical and lesion characteristics, including age, sex, history of chronic kidney disease, history of stroke, severe left ventricular systolic dysfunction (ejection fraction, <30%), ST-segment–elevation myocardial infarction at presentation, intra-aortic balloon pump in cardiogenic shock 2 score, left main or left anterior descending coronary artery as a culprit vessel, culprit lesion TIMI flow grade after PCI, mechanical ventilation, and triple-vessel disease (Table 3). These results were also consistent in the 99 pairs of propensity score–matched population (Figure 2B and Table 3). The explanatory analysis comparing the outcomes between immediate or staged multivessel revascularization versus

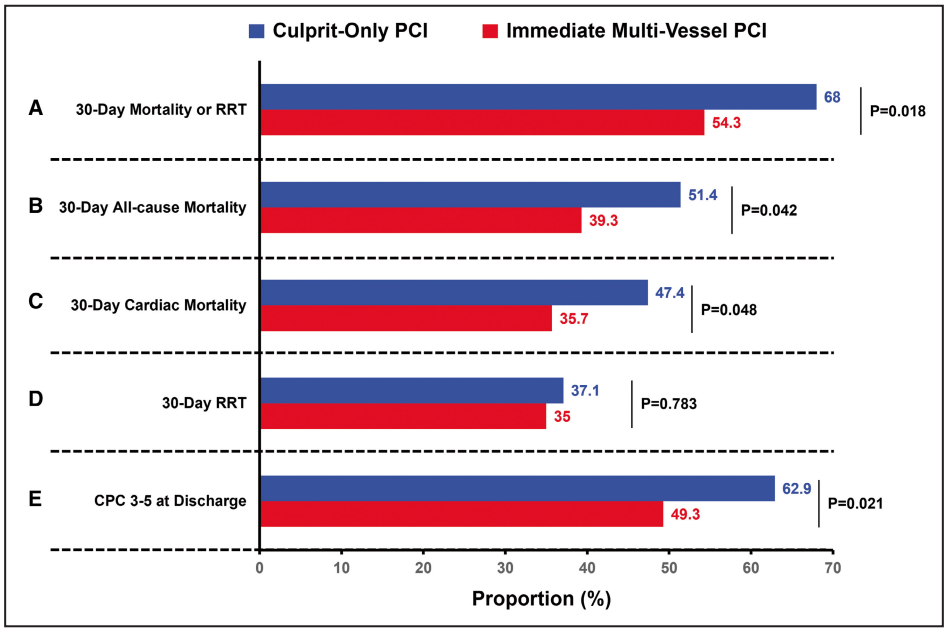

Figure 1. Comparison of short-term outcomes between culprit-only PCI vs multivessel PCI for patients with acute myocardial infarction and multivessel disease complicated by cardiogenic shock undergoing venoarterial-extracorporeal membrane oxygenation before revascularization.
Bar graphs show the rates of short-term clinical outcomes, including 30-day mortality or RRT (**A**), 30-day mortality (**B**), 30-day cardiac mortality (**C**), 30-day RRT (**D**), and CPC 3 to 5 at discharge (**E**) between culprit-only PCI (blue bars) and immediate multivessel PCI (red bars). CPC indicates Cerebral Performance Category; PCI, percutaneous coronary intervention; and RRT, renal-replacement therapy.

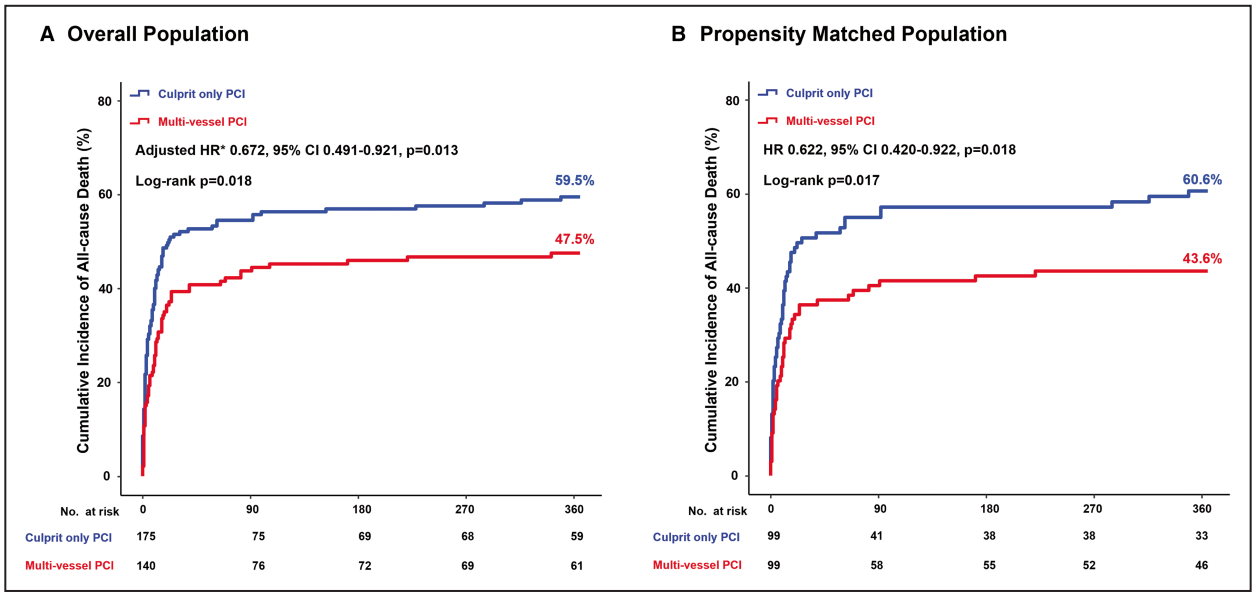

Figure 2. Comparison of 12-month follow-up all-cause mortality between culprit-only PCI vs multivessel PCI for patients with acute myocardial infarction and multivessel disease complicated by cardiogenic shock undergoing venoarterial-extracorporeal membrane oxygenation before revascularization.
Kaplan-Meier curves are shown for comparing 12-month follow-up mortality between the culprit-only (blue line) vs multivessel PCI (red line) groups in the overall population (**A**) and propensity-matched population (**B**). *Adjusted variables included age, sex, history of chronic kidney disease, history of stroke, severe left ventricular systolic dysfunction (ejection fraction, <30%), ST-segment–elevation myocardial infarction, intra-aortic balloon pump in cardiogenic shock 2 score, left main or left anterior descending artery as a culprit vessel, culprit lesion TIMI flow grade after PCI, mechanical ventilation, and triple-vessel disease. HR indicates hazard ratio; PCI, percutaneous coronary intervention; RRT, renal-replacement therapy; and TIMI, Thrombolysis in Myocardial Infarction.

culprit-only revascularization showed similar results (Figure S4).

Subgroup Analysis

The subgroup analyses were performed to identify whether the efficacy of immediate multivessel PCI differed among various subgroups. The lower risk of all-cause mortality up to 12 months in the immediate multivessel PCI was similar across various clinical, lesion severity, or lesion characteristics, without significant interaction (Figure 3).

DISCUSSION

Using patient-pooled data from dedicated cohorts for CS, we compared the short-term and follow-up clinical outcomes between culprit-only versus multivessel PCI in patients with AMI with multivessel disease complicated by an advanced form of CS who underwent VA-ECMO before revascularization. In the current study, we found that the immediate multivessel procedure was significantly associated with lower risks of 30-day mortality or RRT and 12-month all-cause mortality compared with culprit-only PCI in patients with AMI and multivessel disease complicated by CS requiring VA-ECMO before revascularization, and these findings were maintained even in a propensity score–matched population.

In patients who presented with ST-segment–elevation myocardial infarction and multivessel disease without CS, several well-designed randomized trials have consistently demonstrated that complete revascularization (either immediate or staged) was associated with a significantly reduced risk of adverse cardiovascular events compared with culprit-only revascularization.[13,19–22] Conversely, the CULPRIT-SHOCK trial, which is a randomized trial for comparing the outcomes according to the NCL treatment strategies for patients with AMI with CS, identified culprit-only PCI was superior to immediate multivessel PCI with respect to short-term mortality or risk of RRT, in contrast to the previous results of several observational studies.[5,9,23–25] However, in the CULPRIT-SHOCK trial, only 28.3% of patients received MCS devices, including 6.6% of the total cohort who were supported with VA-ECMO. Furthermore, 35.9% of patients had lactate ≤2 mmol/L, and the median systolic blood pressure of the total population was 100 mm Hg. This indicates that many patients with an advanced form of CS may not have been included in this trial. Considering

Table 3. One-Year Follow-Up Outcomes According to Revascularization Strategy

Variable			Univariate analysis			Multivariable analysis*			Propensity-matched analysis (n=198, with 99 pairs)†		
	Culprit-only PCI (N=175)	Multivessel PCI (N=140)	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
All-cause mortality	103 (59.5)	66 (47.5)	0.689	0.506–0.939	0.018	0.672	0.491–0.921	0.013	0.580	0.419–0.804	0.001
Cardiac mortality	95 (56.4)	61 (44.9)	0.692	0.501–0.954	0.025	0.681	0.491–0.944	0.021	0.609	0.437–0.849	0.003
Recurrent MI	1 (0.6)	4 (4.4)	4.413	0.492–39.56	0.185	5.053	0.505–50.51	0.168	2.675	0.143–390.3	0.519
HF rehospitalization	14 (18.8)	13 (17.5)	0.856	0.402–1.822	0.687	0.824	0.408–1.662	0.588	0.580	0.239–1.404	0.227
Repeated revascularization	7 (9.4)	4 (5.4)	0.857	0.297–2.471	0.776	0.766	0.256–2.294	0.634	0.464	0.078–2.768	0.400
Death, MI, or HF rehospitalization	117 (67.9)	80 (57.7)	0.741	0.575–0.955	0.021	0.742	0.573–0.960	0.023	0.546	0.396–0.751	<0.001

Data are given as number (percentage) unless otherwise indicated. The cumulative incidence of clinical outcomes is presented as event number and Kaplan-Meier estimates at 12 months from the index procedure.
HF indicates heart failure; HR, hazard ratio; MI, myocardial infarction; PCI, percutaneous coronary intervention; and TIMI, Thrombolysis in Myocardial Infarction.
*Adjusted variables included age, sex, history of chronic kidney disease, history of stroke, severe left ventricular systolic dysfunction (ejection fraction, <30%), ST-segment–elevation myocardial infarction, intra-aortic balloon pump in cardiogenic shock 2 score, left main or left anterior descending artery as a culprit vessel, culprit lesion TIMI flow grade after PCI, mechanical ventilation, and triple-vessel disease.
†The area under the curve of logit model for treatment group was 0.713 (95% CI, 0.656–0.769).

the recent new 5-stage CS classification (proposed by the Society for Cardiovascular Angiography and Interventions)[26] being clearly associated with robust mortality risk stratification for patients with CS,[27–29] it is unclear whether the role of immediate multivessel PCI differed for an extremely advanced form of CS, which is underreported in the CULPRIT-SHOCK trial. Notably, data from the large US NCDR demonstrated that the benefits of multivessel PCI in patients with non–ST-segment–elevation myocardial infarction and CS were more pronounced in those requiring MCS.[9] Furthermore, in another cohort from the National Cardiogenic Shock Initiative, which emphasized early Impella support with invasive hemodynamic monitoring, multivessel PCI showed comparable clinical outcomes to culprit-only PCI.[23] Taken together, there is a possibility of allowing immediate multivessel PCI through hemodynamic support with MCS, in contrast to CS without MCS support. Nevertheless, there have been limited data on the association between NCL treatment strategy and clinical outcomes in patients with AMI and CS treated with VA-ECMO. Therefore, we conducted the current study to compare the outcomes between culprit-only and immediate multivessel PCI in patients with an advanced form of CS requiring VA-ECMO before revascularization and found that the immediate multivessel PCI was associated with significantly lower risks of 30-day mortality or RRT and 12-month all-cause mortality compared with culprit-only PCI. In the recommendations of previous guidelines based on expert opinions, revascularization for NCL would help in recovering myocardial perfusion and left ventricular function, and these potential benefits might be more prominent in patients with an extremely advanced form of CS. Furthermore, hemodynamic support using MCS devices, including ECMO, might reduce the possibility of temporary exacerbation of CS attributable to additional procedural risks associated with NCL revascularization by maintaining organ perfusion during immediate multivessel PCI. Especially, the clinical role of NCL revascularization may be different from that of other MCS devices capable of left ventricular unloading because VA-ECMO may induce pulmonary edema along with an increase of left ventricular filling pressure by increasing the afterload, which may result in aggravation of the ischemia in the NCL lesion territory and delay the recovery of cardiac function, leading to failure of ECMO weaning.

In the CULPRIT-SHOCK trial, 23.5% of enrolled patients had at least 1 CTO lesion, which required treatment during the index procedure in patients randomized to multivessel PCI; however, the immediate technical success of CTO revascularization was achieved in only 16.6% (13/78) of cases despite the expense of a higher amount of contrast media and longer procedural time.[30] In the present study, in contrast to the CULPRIT-SHOCK

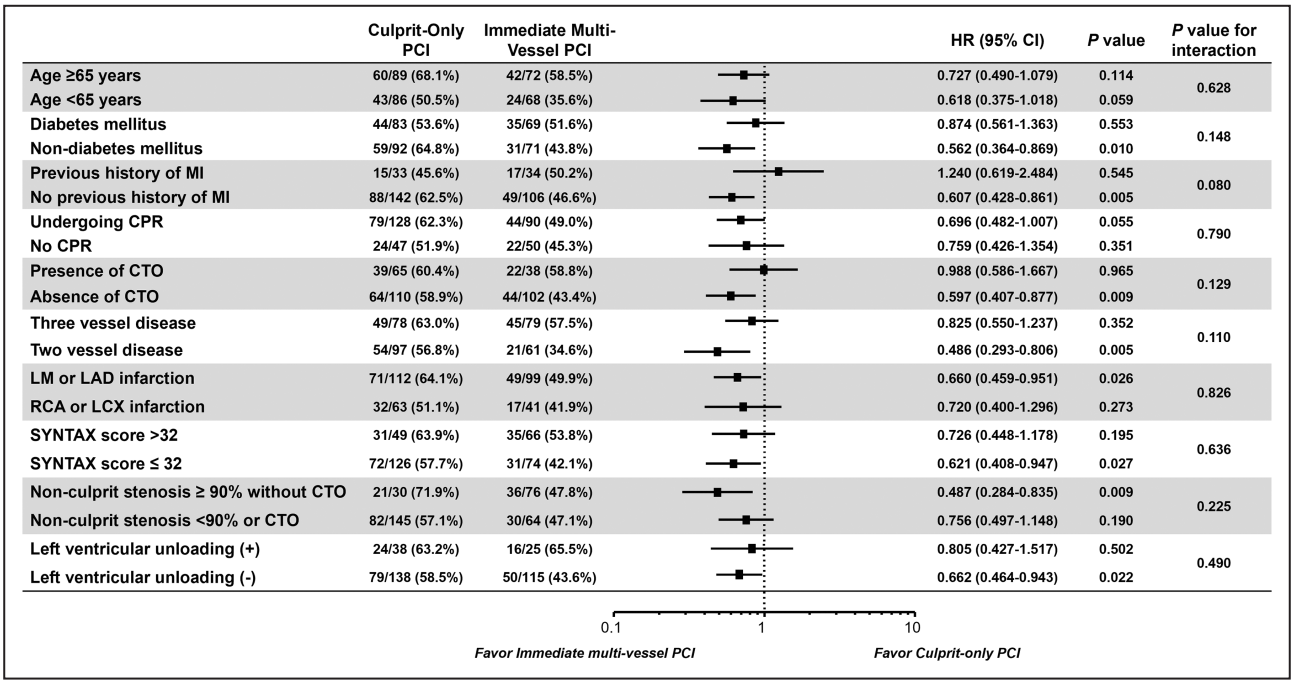

Figure 3. Comparison of 12-month follow-up all-cause mortality between culprit-only PCI vs multivessel PCI according to various subgroups.

Comparative HRs of 12-month follow-up mortality for various subgroups in patients with acute MI and multivessel disease complicated by cardiogenic shock undergoing venoarterial-extracorporeal membrane oxygenation before revascularization. CPR indicates cardiopulmonary resuscitation; CTO, chronic total occlusion; HR, hazard ratio; LAD, left anterior descending artery; LCX, left circumflex artery; LM, left main coronary artery; MI, myocardial infarction; PCI, percutaneous coronary intervention; RCA, right coronary artery; and SYNTAX, Synergy Between PCI With Taxus and Cardiac Surgery.

trial, revascularization was attempted immediately in only 16.5% (17/103) of patients with CTO, and 70.6% (12/17) of these cases achieved successful CTO recanalization. This discrepancy on the CTO PCI strategy may be one factor that can explain the conflicting results between CULPRIT-SHOCK trial and the current study. Moreover, in the CULPRIT-SHOCK trial, 12.5% of those randomized to the culprit-only PCI group underwent immediate multivessel PCI and an additional 21.5% underwent staged or urgent repeated revascularization. In contrast, patients who "crossed over" in the CULPRIT-SHOCK trial would have been categorized as undergoing immediate multivessel PCI in the study. Furthermore, transporting the patient to the catheterization laboratory for staged PCI under ECMO support can be risky and burdensome. In fact, only 10.3% (18/175) of patients in the culprit-only PCI group received staged PCI in our cohorts, which is lower than the rates of staged PCI in the CULPRIT-SHOCK trial. Taken together with the results from the 1-year follow-up study in the CULPRIT-SHOCK trial and the current study, immediate multivessel PCI might be considered to reduce future HF hospitalization or urgent revascularization risk and to improve NCL territory ischemia during VA-ECMO maintenance in patients with AMI and CS with hemodynamic stabilization through VA-ECMO insertion before revascularization. The currently ongoing RESCUE-SHOCK trial (clinicaltrials.gov, NCT05527717) will help to confirm our findings.

Limitations

The current study has some limitations that should be noted. First, this study was derived from patient-pooled observational data; therefore, unmeasured confounding factors could have influenced the study results. In particular, the choice of revascularization strategy and application of VA-ECMO devices was solely left to the operator's discretion, and possibly introduced selection bias. Therefore, the current results should be interpreted as hypothesis generating and should be confirmed in a future well-designed randomized trial. However, in contrast to previous registry-based studies, only immediate multivessel PCI (not including staged multivessel PCI) during the primary procedure was classified as the multivessel PCI group to identify the impact of the initial treatment decision for NCL treatment, in agreement with the scheme of the CULPRIT-SHOCK trial. Second, lesion severity of the NCL was assessed by the angiographic findings alone. Third, the hemodynamic data, including cardiac output, pulmonary capillary wedge pressure, and central venous pressure, which are indicators for recovery from shock, were not available in the current study.

CONCLUSIONS

In the setting of AMI and multivessel disease complicated by CS with VA-ECMO support before revascularization, immediate multivessel PCI was associated with lower risks of 30-day mortality or RRT and 12-month follow-up all-cause mortality. This result suggested that NCL revascularization during primary PCI might be considered in selective scenarios of CS, including patients with an extremely advanced form of CS requiring VA-ECMO before revascularization.

ARTICLE INFORMATION

Received February 10, 2023; accepted April 6, 2023.

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Acknowledgments

We would like to thank Se Young Im, MS, Sang Man Park, MS, and Jimin Park, MS, for performing angiographic core laboratory analysis.

Sources of Funding

This study was supported by an unrestricted grant from the Korean Society of Interventional Cardiology (grant number 2016-1).

Disclosures

None.

Supplemental Material

Data S1

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SUPPLEMENTAL MATERIAL

Table S1. Standardized differences of variables used in propensity matching according to treatment strategy.

	Standardized mean difference before propensity matching (N=315)	Standardized mean difference after propensity matching (N=198)
Age, years	-0.7	-5.4
Male	--2.4	4.9
Body mass index > 25 kg/m^2	-4.3	0
Hypertension	12.2	-8.2
Diabetes mellitus	3.7	-6.1
Dyslipidemia	3.5	-2.5
Chronic kidney disease	9.0	-9.5
Current smoking	2.2	4.4
Previous myocardial infarction	12.7	2.4
Peripheral artery disease	-13.7	-6.1
Previous history of stroke	-6.9	3.8
STEMI at presentation	-12.5	2.1
IABP-SHOCK 2 score	-18.9	-5.8
Undergoing CPR	-18.5	-4.2
Mechanical ventilation	-0.9	6.0
Vasopressor use	5.4	-5.4
Combined IABP insertion	-10.1	3.1
LM or LAD as a culprit vessel	14.8	2.2
Triple vessel disease	23.8	4.1

Number of lesions	32.6	-1.6
SYNTAX score, pre-PCI	41.5	-3.0
Non-culprit CTO lesion	-22.5	0

CPR= cardiopulmonary resuscitation; CTO, chronic total occlusion; IABP= intra-aortic balloon pump; IABP-SHOCK= Intra-aortic Balloon Pump in Cardiogenic Shock; LAD, left anterior descending artery; LM, left main coronary artery; STEMI= ST-segment elevation myocardial infarction; SYNTAX= Synergy between PCI with Taxus and Cardiac Surgery.

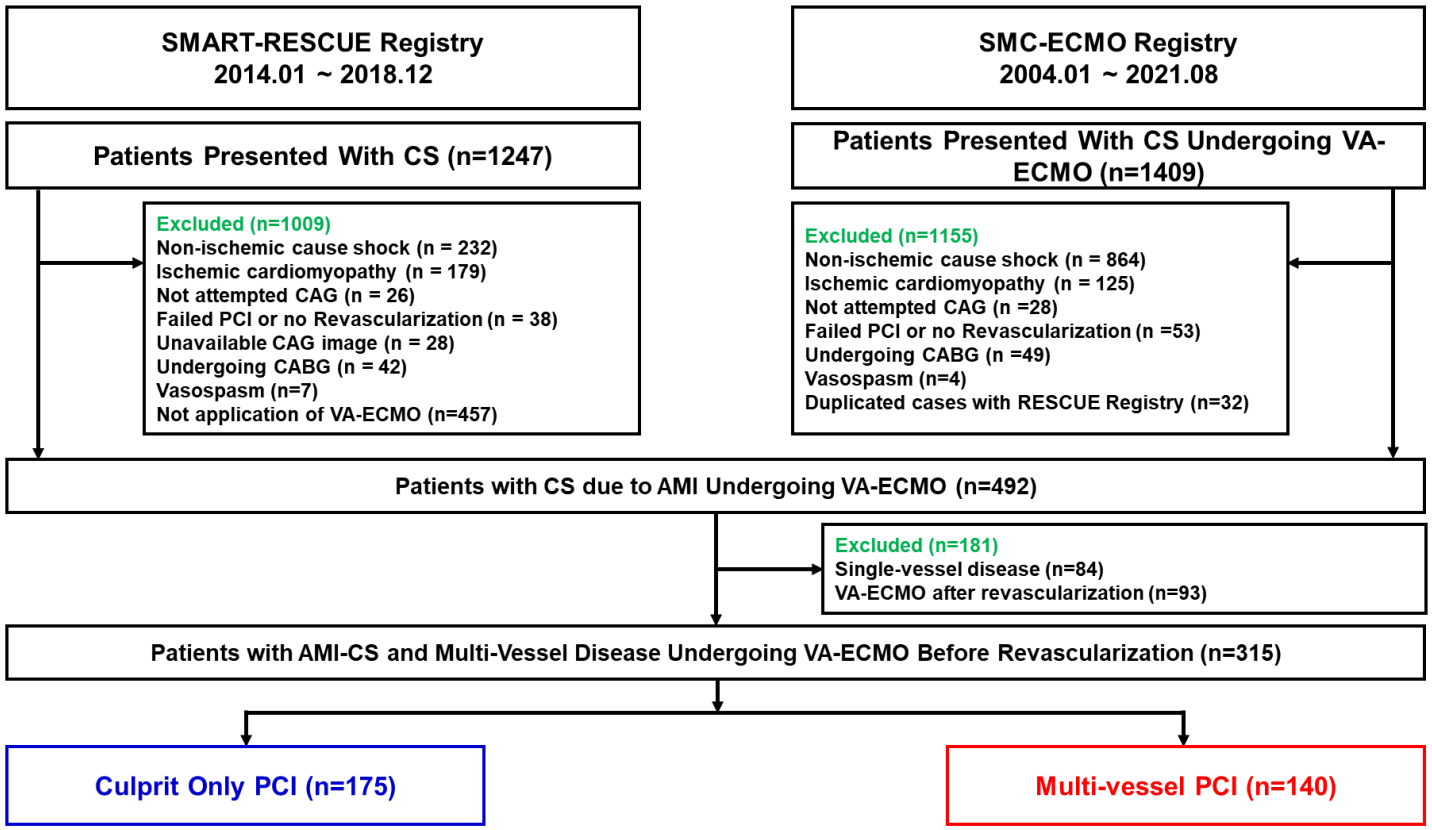

Figure S1. Study Flow

AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; CAG, coronary angiography; CS, cardiogenic shock; PCI, percutaneous coronary intervention; VA-ECMO, venoarterial-extracorporeal membrane oxygenation.

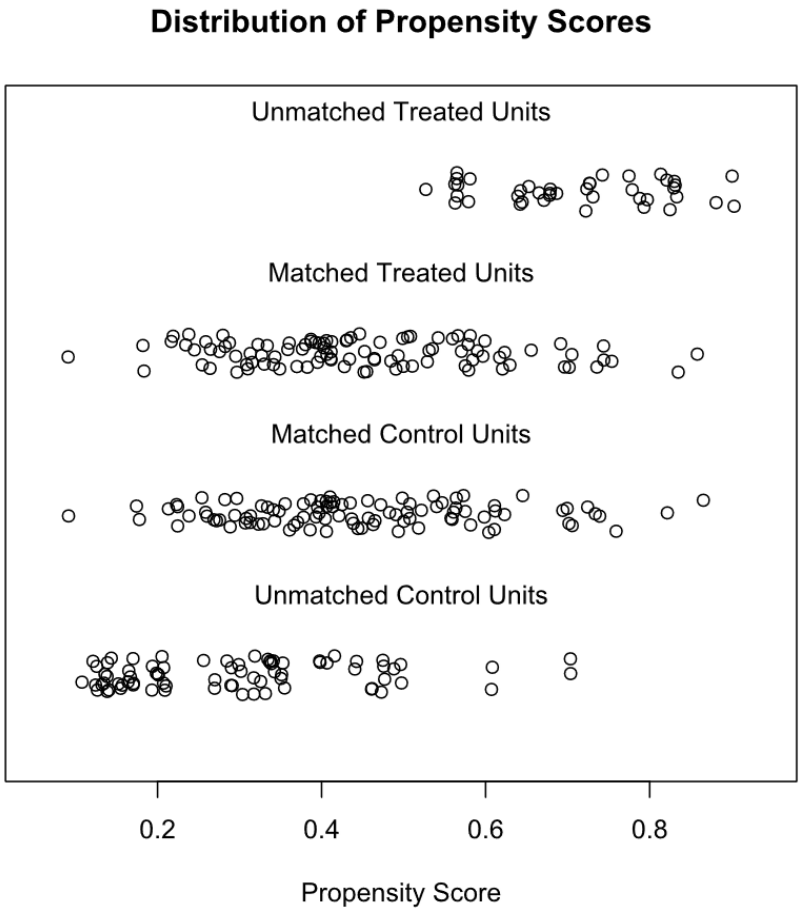

Figure S2. Balance Plot for Propensity Matching

The balance of the propensity score was plotted.

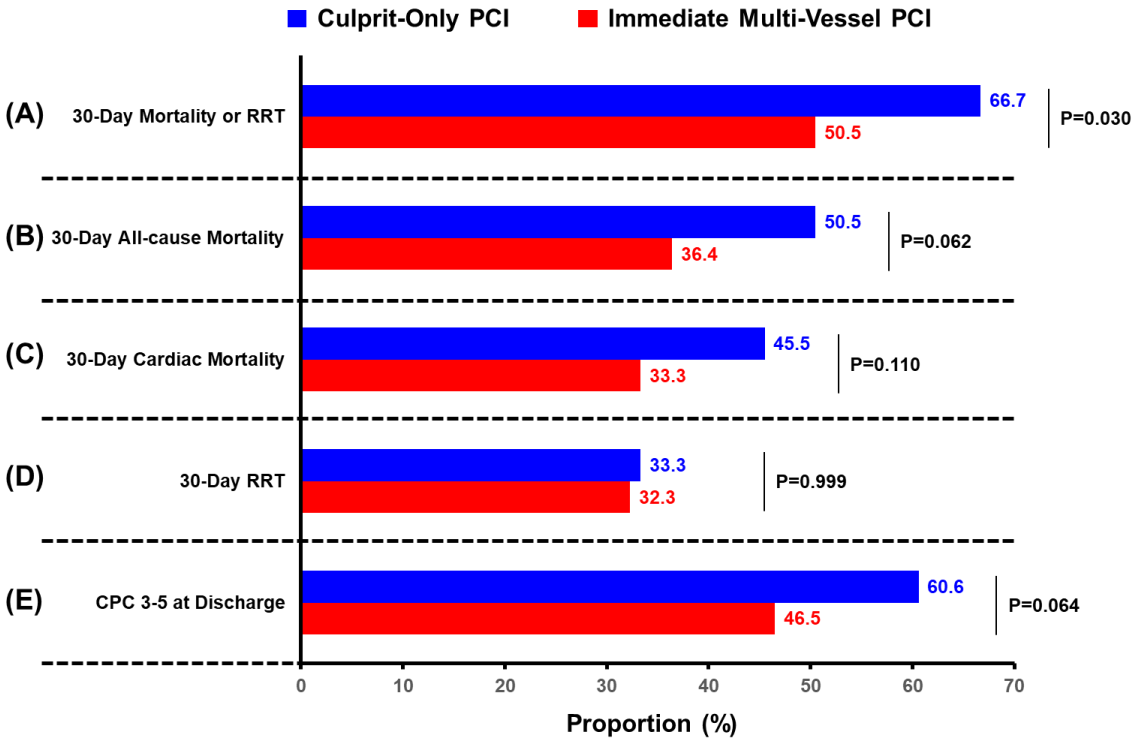

Figure S3. Comparison of Short-term Outcomes Between Culprit-Only PCI versus Multi-vessel PCI in Propensity-Matched Population

Bar graphs show the rates of short-term clinical outcomes including (A) 30-day mortality or RRT, (B) 30-day mortality, (C) 30-day cardiac mortality, (D) 30-day RRT, and (E) CPC 3-5 at discharge between culprit-only PCI (blue bars) and immediate multi-vessel PCI (red bars) in propensity-matched population.

CPC, Cerebral Performance Category; PCI, percutaneous coronary intervention; RRT, renal-replacement therapy; VA-ECMO, venoarterial-extracorporeal membrane oxygenation.

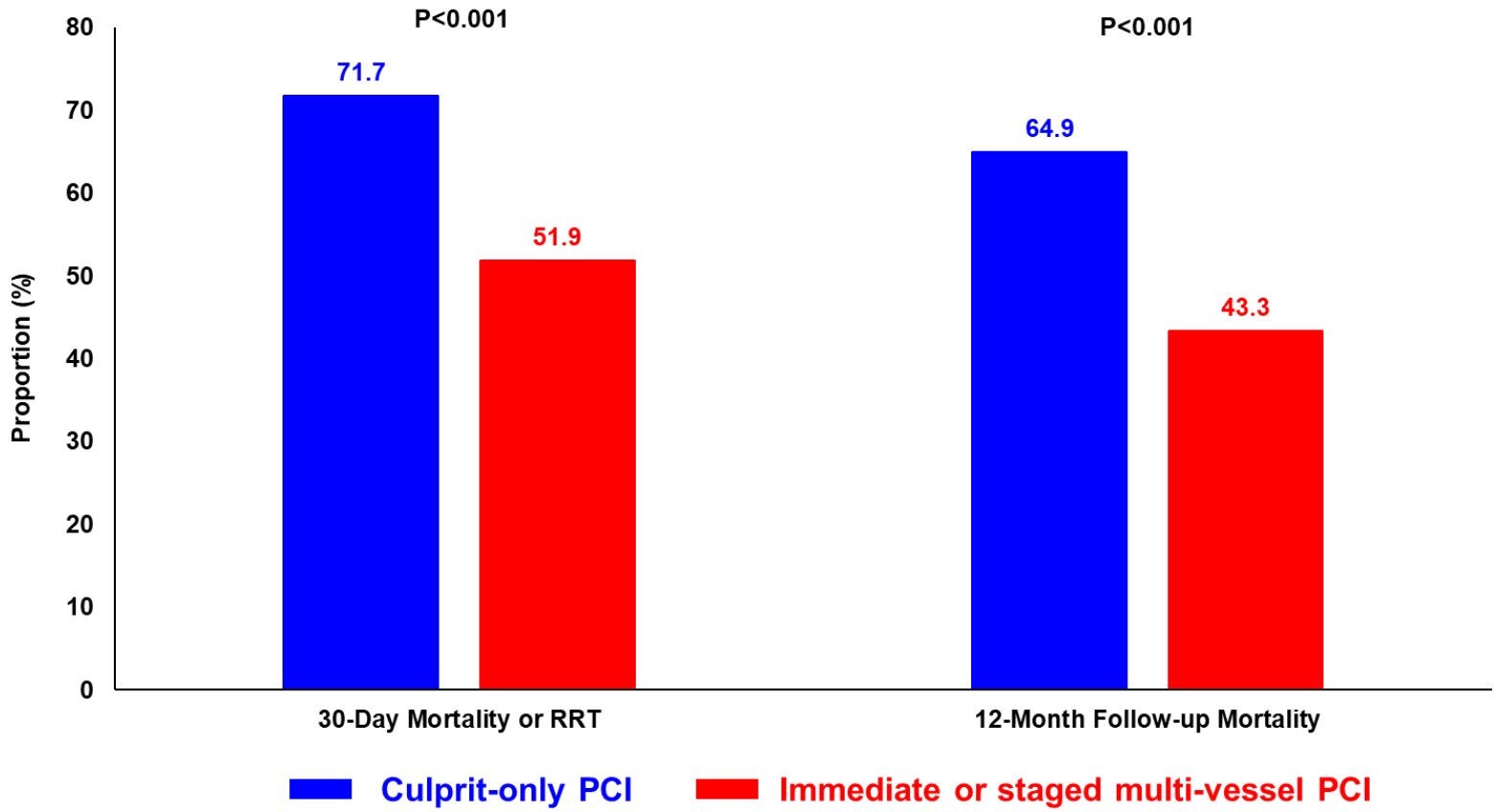

Figure S4. Explanatory Analyses Comparing Immediate or Staged Multi-vessel Revascularization vs. Culprit-only Revascularization.

PCI, percutaneous coronary intervention; RRT, renal replacement therapy.