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Long-term clinical outcomes in patients with acute myocardial infarction complicated by cardiogenic shock according to the application and initiation time of extracorporeal membrane oxygenation in South Korea

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Abstract

Background: *Limited data are available regarding the proper application time and long-term outcomes of extracorporeal membrane oxygenation (ECMO) in patients with cardiogenic shock. This cohort study appraised the clinical outcomes according to ECMO application without or before cardiopulmonary resuscitation (CPR) in patients with acute myocardial infarction (AMI) combined with cardiogenic shock.*

Methods: *Between 2011 and 2015, a total of 13,104 patients with AMI were enrolled in a nationwide AMI registry. Eligible patients with cardiogenic shock, who underwent percutaneous coronary intervention, with a 3-year clinical follow-up, were analyzed. The 949 included patients were divided into two groups: no ECMO (n = 845) and ECMO application (n = 104). The ECMO group was further divided into ECMO without or before CPR (n = 11) and ECMO after CPR (n = 93).*

Results: *Significant differences were noted in major adverse cardiac events (MACEs) between the no ECMO and ECMO application groups during the 3-year follow-up (41.5% vs. 80.8%; p < 0.001). However, the ECMO without or before CPR group showed similar outcomes to the no ECMO group in 3-year MACEs (63.6% vs. 41.5%; p = 0.055). MACEs during 3 years of follow-up were significantly lower in the ECMO without or before CPR group than in the ECMO after CPR group (63.6% vs. 82.8%; p = 0.005).*

Conclusions: *A significantly lower risk of major cardiac events in ECMO without or before CPR suggests that early application of ECMO can be a reasonable strategy to improve outcomes in patients with AMI complicated by cardiogenic shock.* (Cardiol J 2023; 30, 5: 713–724)

Key words: cardiogenic shock, cardiopulmonary resuscitation, extracorporeal membrane oxygenation, myocardial infarction, percutaneous coronary intervention

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Introduction

Acute myocardial infarction (AMI) complicated by cardiogenic shock is an emergency situation requiring immediate invasive therapeutic strategy [1]. Although early revascularization of the culprit lesion in the coronary artery yields significant survival gains, cardiogenic shock remains unresolved in many cases [2]. The application of extracorporeal membrane oxygenation (ECMO) can be considered in patients with AMI complicated by cardiogenic shock, who have not improved with medical treatment or intra-aortic balloon pump application. The 2020 European Society of Cardiology guidelines for patients without persistent ST-segment elevation recommended a short period of percutaneous mechanical circulatory support in selected patients with acute coronary syndrome complicated by cardiogenic shock [1]. Several reports on ECMO application in patients with AMI complicated by cardiogenic shock support this guideline. ECMO-assisted cardiopulmonary resuscitation (CPR) demonstrates better clinical outcomes than conventional CPR in patients with in-hospital cardiac arrest of cardiac origin [3]. Early application of ECMO has improved the survival among patients with AMI complicated by profound shock [4]. However, optimal application times and long-term clinical outcomes for ECMO remain unclear.

This study evaluated the 3-year clinical outcomes of patients with AMI complicated by cardiogenic shock according to the application and initiation time of ECMO.

Methods

This study was based on the Korean Acute Myocardial Infarction Registry – National Institutes of Health; a nationwide, prospective, observational multicenter registry including 20 large medical institutions/university hospitals. The collected clinical data were managed through the National Institute of Health's Clinical Research and Trial Management System. All data were entered by research coordinators who have undergone professional training. The data input method of the coordinator, a regular progress check, and the registration status were thoroughly monitored. All patients provided written informed consent before enrollment in this study. This study was performed following the Declaration of Helsinki. Each institution gave ethical approval. The institutional review board approval number was CNUH-2011-172, Chonnam National University Hospital.

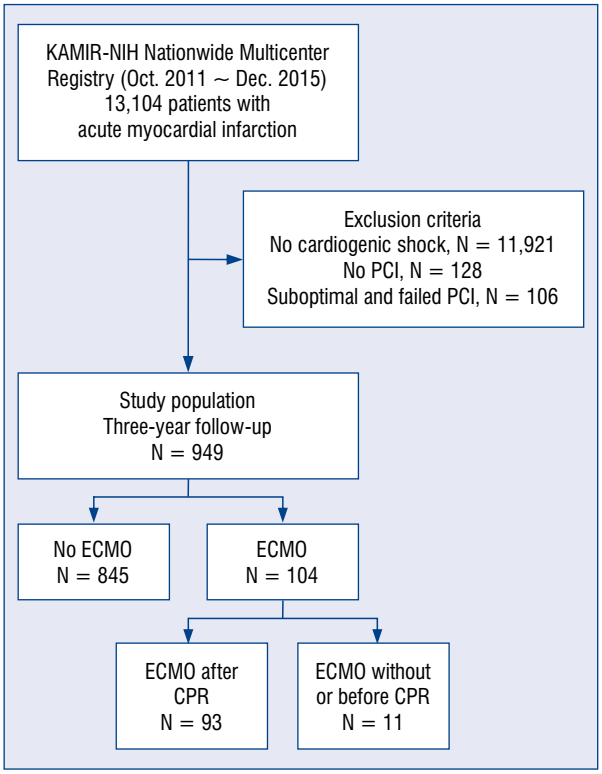


Figure 1. Study flow chart. This study population was based on the nationwide, multicenter, prospective, observational KAMIR-NIH registry; CPR — cardiopulmonary resuscitation; ECMO — extracorporeal membrane oxygenation; KAMIR-NIH — Korea Acute Myocardial Infarction Registry – National Institutes of Health; PCI — percutaneous coronary intervention.

Among 13,104 patients with AMI registered in the Korean Acute Myocardial Infarction Registry – National Institutes of Health between November 2011 and December 2015, 949 with cardiogenic shock, who underwent successful percutaneous coronary intervention (PCI) were included in the study (Fig. 1). Cardiogenic shock is defined as systolic blood pressure < 90 mmHg for > 30 min even with adequate filling status with signs of hypoperfusion and at least one of the following: cold sweaty extremities, oliguria, mental confusion, metabolic acidosis, elevated serum lactate, and elevated serum creatinine [5–9]. Exclusion criteria were no cardiogenic shock, no PCI, and suboptimal/failed PCI.

The study population was divided into two groups depending on ECMO use: a no ECMO application group (n = 845) and an ECMO application group (n = 104). The ECMO application group was further divided into two groups according to whether or when they underwent CPR: an ECMO

application after CPR group (n = 93) and an ECMO application without or before CPR group (n = 11). Only 1 patient underwent ECMO application before CPR among 11 patients. The interval between the two events was 38 days.

All medical treatments and procedures were conducted following the myocardial infarction guidelines. Dual antiplatelet therapy, a combination of acetylsalicylic acid and a P_2Y_{12} inhibitor, was administered before the intervention. After coronary angiography, PCI was performed based on the decision of the individual operator. Successful PCI was defined as residual stenosis of the culprit lesion of < 30% and a Thrombolysis in Myocardial Infarction grade of III. The operator also determined the use of other equipment, including ECMO application. After the procedure, statins, beta-blockers, and renin–angiotensin system inhibitors were administered according to patient condition. In-hospital complications, such as acute heart failure, acute kidney injury, and major bleeding, were also investigated at admission. Major bleeding was defined according to the Thrombolysis in Myocardial Infarction Trial, as an intracranial hemorrhage or hemoglobin decrease of > 5 g/dL (or 15% in hematocrit) [10]. Follow-up for patients was conducted at 6 months and 1, 2, and 3 years from the discharge date. Follow-up examinations, including blood tests, echocardiography, and coronary angiography, were performed at the physician's discretion.

The primary outcome was a major adverse cardiac event (MACE) (all-cause death [cardiac and non-cardiac], spontaneous myocardial infarction, repeat PCI, coronary artery bypass graft) at 3 years. The secondary endpoints were all-cause death, cardiac death, spontaneous myocardial infarction, and repeat revascularization at 3 years. Spontaneous myocardial infarction was defined as elevated levels of cardiac enzymes over the 99th percentile of the upper reference limit with typical chest pain or an electrocardiogram change. Repeat revascularization is considered ischemia-driven revascularization, involving repeat PCI and coronary artery bypass grafting. The definitions of all these cardiac events were based on the Academic Research Consortium [11].

Categorical data are expressed in counts and percentages. A chi-square test was used to evaluate the significance of the two variables. Fischer's exact test was used when > 20% of cells had an expected count < 5. Continuous variables were represented by means and standard variances. Student's t-test was used to evaluate the significance of the two variables. Normality distribution was determined with the Kolmogorov–Smirnov and Shapiro–Wilk tests. If the two variables were not normally distributed, the Mann–Whitney test was used. Kaplan–Meier curve analysis was performed to calculate cumulative event rates. The survival rates of the two groups were compared using the log-rank test. Univariable analysis was performed by inserting variables into the Cox proportional hazards model. In multivariable analysis, clinically relevant variables with a p-value < 0.05 in univariable analysis were inserted into the multivariable Cox model. The following variables included in the multivariable analysis had missing values: current smoker (n = 26), left ventricular ejection fraction (n = 156), and creatinine (n = 1). Statistical significance was determined with a 2-tailed test and was considered significant at $p < 0.05$. The 95% confidence intervals (CI) and hazard ratios (HR) were estimated by Cox regression. All statistical analyses were performed using IBM® SPSS® Statistics, version 25.0.

Results

All patients were monitored for 3 years; the median follow-up duration was 689 days. Baseline clinical characteristics of the patients, initial laboratory findings at admission, and medications administered during hospitalization are summarized in Table 1. Although patients in the ECMO application group were younger than those in the no ECMO application group, they had more Killip class ≥ 3 (72.1% vs. 46.6%; $p < 0.001$), ST-segment elevation myocardial infarction (80.8% vs. 71.6%; $p < 0.048$) at initial presentation, lower blood pressure, and lower left ventricular ejection fraction (34.0% vs. 48.2%; $p < 0.001$). Moreover, the ECMO application group showed higher myocardial enzyme levels and took fewer medicines, such as angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, beta-blockers, and statins. A comparison of the findings of the ECMO application without or before CPR group and ECMO application after CPR group revealed that they were similar, although the ECMO application without or before CPR group revealed higher heart rates, and the group members were administered more statins than those in the ECMO application after CPR group.

Baseline procedural findings and the development of in-hospital complications are summarized in Table 2. The proportion of patients with the left main coronary artery as the culprit vessel was higher in the ECMO application group than in

Table 1. Baseline clinical characteristics of the patients, initial laboratory findings, and medications administered during admission.

	Total (n = 949)	No ECMO (n = 845)	ECMO (n = 104)	P	Total (n = 104)	ECMO without or before CPR (n = 11)	ECMO after CPR (n = 93)	P
Demographics								
Age [years]	67.1 ± 12.4	67.6 ± 12.4	63.3 ± 11.8	0.001	63.3 ± 11.8	60.3 ± 13.2	63.6 ± 11.6	0.374
Age > 75 years	310 (32.7%)	290 (34.3%)	20 (19.2%)	0.002	20 (19.2%)	3 (27.3%)	17 (18.3%)	0.439
Male	684 (72.1%)	603 (71.4%)	81 (77.9%)	0.162	81 (77.9%)	8 (72.7%)	73 (78.5%)	0.704
Body mass index [kg/m^2]	23.3 ± 3.3	23.2 ± 3.2	24.3 ± 3.9	0.004	24.3 ± 3.9	24.8 ± 3.1	24.2 ± 4.0	0.201
Initial presentation								
Killip class ≥ 3	469 (49.4%)	394 (46.6%)	75 (72.1%)	< 0.001	75 (72.1%)	6 (54.5%)	69 (74.2%)	0.169
SBP [mmHg]	100.5 ± 39.8	101.7 ± 39.9	90.5 ± 38.2	0.008	90.5 ± 38.2	102.8 ± 17.7	89.0 ± 39.8	0.140
DBP [mmHg]	61.8 ± 26.5	62.5 ± 26.4	56.2 ± 26.8	0.024	56.2 ± 26.8	66.8 ± 13.5	54.9 ± 27.8	0.077
Heart rate [bpm]	77.7 ± 30.7	77.4 ± 30.3	80.9 ± 33.8	0.272	80.9 ± 33.8	100.5 ± 28.3	78.5 ± 33.7	0.041
STEMI	689 (72.6%)	605 (71.6%)	84 (80.8%)	0.048	84 (80.8%)	8 (72.7%)	76 (81.7%)	0.439
Process of care index								
Symptom onset-to--door time [h]	15.1 ± 61.2	15.6 ± 64.3	10.7 ± 25.6	0.439	10.7 ± 25.6	8.5 ± 13.1	11.0 ± 26.7	0.410
Door-to-balloon time [h]	7.8 ± 27.6	8.0 ± 27.7	6.0 ± 27.0	0.488	6.0 ± 27.0	27.0 ± 77.3	3.6 ± 10.3	0.196
Cardiovascular risk factors								
Family history	49 (5.3%)	42 (5.1%)	7 (7.1%)	0.406	7 (7.1%)	1 (10.0%)	6 (6.7%)	0.537
Hypertension	489 (51.5%)	435 (51.5%)	54 (51.9%)	0.932	54 (51.9%)	6 (54.5%)	48 (51.6%)	0.854
Diabetes mellitus	311 (32.8%)	274 (32.4%)	37 (35.6%)	0.518	37 (35.6%)	7 (63.6%)	30 (32.3%)	0.051
Dyslipidemia	82 (8.6%)	75 (8.9%)	7 (6.7%)	0.463	7 (6.7%)	0 (0.0%)	7 (7.5%)	1.000
Previous history of MI	71 (7.5%)	64 (7.6%)	7 (6.7%)	0.758	7 (6.7%)	0 (0.0%)	7 (7.5%)	1.000
Previous history of CHF	27 (2.9%)	25 (3.0%)	2 (2.0%)	0.759	2 (2.0%)	0 (0.0%)	2 (2.2%)	1.000
Previous history of CVA	75 (8.0%)	71 (8.5%)	4 (3.8%)	0.123	4 (3.8%)	0 (0.0%)	4 (4.3%)	1.000
Current smoker	353 (38.2%)	312 (37.8%)	41 (42.3%)	0.389	41 (42.3%)	5 (50.0%)	36 (41.4%)	0.601
LVEF [%]	47.0 ± 13.1	48.2 ± 12.4	34.0 ± 14.0	< 0.001	34.0 ± 14.0	33.9 ± 8.9	34.1 ± 14.8	0.965
Laboratory findings								
Creatinine [mg/dL]	1.4 ± 1.4	1.3 ± 1.3	1.6 ± 1.9	0.076	1.6 ± 1.9	1.1 ± 0.3	1.6 ± 2.0	0.150
Peak troponin I [mg/mL]	88.3 ± 138.4	74.8 ± 112.8	190.8 ± 237.5	<0.001	190.8 ± 237.5	166.0 ± 172.0	193.2 ± 243.5	0.487
Peak CK-MB [ng/mL]	196.9 ± 221.6	176.8 ± 173.0	363.2 ± 422.4	< 0.001	363.2 ± 422.4	247.5 ± 207.0	375.7 ± 438.3	0.283
Medications								
ASA	944 (99.5%)	842 (99.6%)	102 (98.1%)	0.095	102 (98.1%)	11 (100.0%)	91 (97.8%)	1.000
Clopidogrel	745 (78.5%)	670 (79.3%)	75 (72.1%)	0.093	75 (72.1%)	7 (63.6%)	68 (73.1%)	0.495
Prasugrel	127 (13.4%)	108 (12.8%)	19 (18.3%)	0.121	19 (18.3%)	3 (27.3%)	16 (17.2%)	0.418
Ticagrelor	199 (21.0%)	181 (21.4%)	18 (17.3%)	0.331	18 (17.3%)	2 (18.2%)	16 (17.2%)	1.000
ACEI or ARB	501 (52.8%)	477 (56.4%)	24 (23.1%)	< 0.001	24 (23.1%)	4 (36.4%)	20 (21.5%)	0.273
Beta-blocker	535 (56.4%)	508 (60.1%)	27 (26.0%)	< 0.001	27 (26.0%)	4 (36.4%)	23 (24.7%)	0.470
Statin	641 (67.5%)	607 (71.8%)	34 (32.7%)	< 0.001	34 (32.7%)	9 (81.8%)	25 (26.9%)	0.001
Oral anticoagulant	38 (4.0%)	35 (4.1%)	3 (2.9%)	0.790	3 (2.9%)	0 (0.0%)	3 (3.2%)	1.000

Values are mean ± standard deviation or number (%). Among total study population, values for body mass index are missing in 72 cases, SBP in 84 cases, DBP in 101 cases, heart rate in 48 cases, familial history in 25 cases, previous history of CHF in 5 cases, previous history of CVA in 7 cases, current smoker in 26 cases, LVEF in 156 cases, creatinine in 1 case, peak troponin I in 170 cases, and peak CK-MB in 3 cases.
ACEI — angiotensin-converting enzyme inhibitor; ASA — acetylsalicylic acid; ARB — angiotensin receptor blocker; CHF — congestive heart failure; CK-MB — creatine kinase-myocardial band; CVA — cerebrovascular accident; DBP — diastolic blood pressure; ECMO — extracorporeal membrane oxygenation; LVEF — left ventricular ejection fraction; MI — myocardial infarction; SBP — systolic blood pressure; STEMI — ST-segment elevation myocardial infarction

Table 2. Baseline procedure findings and development of in-hospital complications.

	Total (n = 949)	No ECMO (n = 845)	ECMO (n = 104)	P	Total (n = 104)	ECMO without or before CPR (n = 11)	ECMO after CPR (n = 93)	P
Culprit lesion profiles								
Location:								
Left main artery	63 (6.6%)	37 (4.4%)	26 (25.0%)	< 0.001	26 (25.0%)	2 (18.2%)	24 (25.8%)	0.727
LAD	416 (43.8%)	373 (44.1%)	43 (41.3%)	0.588	43 (41.3%)	7 (63.6%)	36 (38.7%)	0.193
LCX	119 (12.5%)	101 (12.0%)	18 (17.3%)	0.120	18 (17.3%)	1 (9.1%)	17 (18.3%)	0.685
RCA	351 (37.0%)	334 (39.5%)	17 (16.3%)	< 0.001	17 (16.3%)	1 (9.1%)	16 (17.2%)	0.687
Type B2/C lesion*	875 (92.2%)	779 (92.2%)	96 (92.3%)	0.966	96 (92.3%)	9 (81.8%)	87 (93.5%)	0.200
Overall lesion profiles								
Left main artery disease	92 (9.7%)	60 (7.1%)	32 (30.8%)	< 0.001	32 (30.8%)	3 (27.3%)	29 (31.2%)	1.000
3-vessel disease	185 (19.5%)	171 (20.2%)	14 (13.5%)	0.100	14 (13.5%)	2 (18.2%)	12 (12.9%)	0.641
Procedural characteristics								
Transradial approach	119 (12.5%)	108 (12.8%)	11 (10.6%)	0.522	11 (10.6%)	2 (18.2%)	9 (9.7%)	0.328
Glycoprotein IIb/IIIa inhibitor use	250 (26.3%)	224 (26.5%)	26 (25.0%)	0.742	26 (25.0%)	2 (18.2%)	24 (25.8%)	0.727
Thrombus aspiration	297 (31.3%)	270 (32.0%)	27 (26.0%)	0.214	27 (26.0%)	5 (45.5%)	22 (23.7%)	0.119
IRA treatment								
BMS	72 (7.6%)	60 (7.1%)	12 (11.5%)	0.107	12 (11.5%)	0 (0.0%)	12 (12.9%)	0.355
EES	452 (47.6%)	401 (47.5%)	51 (49.0%)	0.760	51 (49.0%)	9 (81.8%)	42 (45.2%)	0.027
ZES	182 (19.2%)	161 (19.1%)	21 (20.2%)	0.781	21 (20.2%)	0 (0.0%)	21 (22.6%)	0.115
BES	146 (15.4%)	134 (15.9%)	12 (11.5%)	0.249	12 (11.5%)	2 (18.2%)	10 (10.8%)	0.612
SES	25 (2.6%)	21 (2.5%)	4 (3.8%)	0.343	4 (3.8%)	0 (0.0%)	4 (4.3%)	1.000
NES	10 (1.1%)	10 (1.2%)	0 (0.0%)	0.613	0 (0.0%)	0 (0.0%)	0 (0.0%)	
PES	11 (1.2%)	11 (1.3%)	0 (0.0%)	0.621	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Other stents	5 (0.5%)	5 (0.6%)	0 (0.0%)	1.000	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Plain balloon angioplasty	59 (6.2%)	53 (6.3%)	6 (5.8%)	0.841	6 (5.8%)	1 (9.1%)	5 (5.4%)	0.498
Stent diameter [mm]	3.1 ± 0.4	3.2 ± 0.5	3.1 ± 0.4	0.037	3.1 ± 0.4	3.0 ± 0.4	3.1 ± 0.4	0.635
Stent length [mm]	24.8 ± 7.4	24.9 ± 7.3	24.1 ± 8.1	0.337	24.1 ± 8.1	24.6 ± 7.2	24.1 ± 8.2	0.734
Pre-PCI TIMI flow in culprit lesion ≤ 1	643 (67.8%)	570 (67.5%)	73 (70.2%)	0.573	73 (70.2%)	7 (63.6%)	66 (71.0%)	0.729
Post-PCI TIMI flow 3	949 (100.0%)	845 (100.0%)	104 (100.0%)		104 (100.0%)	11 (100.0%)	93 (100.0%)	
IVUS during PCI	155 (16.3%)	147 (17.4%)	8 (7.7%)	0.012	8 (7.7%)	0 (0.0%)	8 (8.6%)	0.595
OCT during PCI	8 (0.8%)	8 (0.9%)	0 (0.0%)	1.000	0 (0.0%)	0 (0.0%)	0 (0.0%)	
IABP use	276 (29.1%)	226 (26.7%)	50 (48.1%)	< 0.001	50 (48.1%)	5 (45.5%)	45 (48.4%)	0.854
In-hospital complications								
Acute heart failure	149 (15.7%)	123 (14.6%)	26 (25.0%)	0.006	26 (25.0%)	3 (27.3%)	23 (24.7%)	1.000
Re-infarction	16 (1.7%)	12 (1.4%)	4 (3.8%)	0.088	4 (3.8%)	0 (0.0%)	4 (4.3%)	1.000
Stent thrombosis	14 (1.5%)	11 (1.3%)	3 (2.9%)	0.191	3 (2.9%)	0 (0.0%)	3 (3.2%)	1.000
Major bleeding								
Intracranial hemorrhage	65 (6.8%)	35 (4.1%)	30 (28.8%)	< 0.001	30 (28.8%)	2 (18.2%)	28 (30.1%)	0.505
Hb decrease†	53 (5.6%)	36 (4.3%)	17 (16.3%)	< 0.001	17 (16.3%)	1 (9.1%)	16 (17.2%)	0.687
Hct decrease‡	5 (0.5%)	2 (0.2%)	3 (2.9%)	0.011	3 (2.9%)	0 (0.0%)	3 (3.2%)	1.000
Minor bleeding	94 (9.9%)	79 (9.3%)	15 (14.4%)	0.102	15 (14.4%)	1 (9.1%)	14 (15.1%)	1.000
Atrial fibrillation	147 (15.5%)	134 (15.9%)	13 (12.5%)	0.372	13 (12.5%)	2 (18.2%)	11 (11.8%)	0.625
Sepsis	34 (3.6%)	29 (3.4%)	5 (4.8%)	0.476	5 (4.8%)	2 (18.2%)	3 (3.2%)	0.086
CPR	458 (48.3%)	364 (43.1%)	94 (90.4%)	< 0.001	94 (90.4%)	1 (9.1%)	93 (100.0%)	< 0.001
MOF	56 (5.9%)	39 (4.6%)	17 (16.3%)	< 0.001	17 (16.3%)	0 (0.0%)	17 (18.3%)	0.204
Defibrillation	282 (29.7%)	226 (26.7%)	56 (53.8%)	< 0.001	56 (53.8%)	4 (36.4%)	52 (55.9%)	0.338
Acute kidney injury	51 (5.4%)	36 (4.3%)	15 (14.4%)	< 0.001	19 (14.4%)	1 (9.1%)	14 (15.1%)	1.000

Values are mean ± standard deviation or number (%). *Type B2 or C lesions according to the ACC/AHA classification. †Hb decrease denotes a decline in Hb of at least 5.0 g/dL. ‡Hct decrease denotes a decline in Hct of at least 15%. BES — biolimus-eluting stent; BMS — bare metal stent; CPR — cardiopulmonary resuscitation; ECMO — extracorporeal membrane oxygenation; EES — everolimus-eluting stent; Hb — hemoglobin; Hct — hematocrit; IABP — intra-aortic balloon pump; IRA — infarct-related artery; IVUS — intravascular ultrasound; LAD — left anterior descending artery; LCX — left circumflex artery; MOF — multi-organ failure; NES — novolimus-eluting stent; OCT — optical coherence tomography; PES — paclitaxel-eluting stent; PCI — percutaneous coronary intervention; RCA — right coronary artery; SES — sirolimus-eluting stent; TIMI — Thrombolysis in Myocardial Infarction; ZES — zotarolimus-eluting stent

the no ECMO application group (25.0% vs. 4.4%; p < 0.001). The ECMO application group received smaller diameter stents (3.1 ± 0.4 mm vs. 3.2 ± ± 0.5 mm; p = 0.037) and more frequent intra-aortic balloon pump application (48.1% vs. 26.7%; p < 0.001) than the no ECMO application group. However, intravascular ultrasound-guided PCI was performed less in the ECMO application group (7.7% vs. 17.4%; p = 0.012). In-hospital complications were more common in the ECMO application group than in the no ECMO application group. A comparison of the ECMO application without or before CPR group and ECMO application after CPR group revealed that their procedural findings and development of in-hospital complications were similar. The ECMO without or before CPR group received everolimus-eluting stents (81.8% vs. 45.2%; p = 0.027) more frequently than the ECMO after CPR group; this was the only difference.

At 3 years, the ECMO application group had a higher risk of MACEs (80.8% vs. 41.5%; HR 2.49 [95% CI 1.74–3.56]; p < 0.001) than the no ECMO application group. The risks of all-cause death and cardiac death were also significantly higher in the ECMO application group. A comparison of the ECMO application without or before CPR group and ECMO application after CPR group showed that the risk of MACEs was lower in the ECMO application without or before CPR group (63.6% vs. 82.8%; HR 2.33 [95% CI 1.07–5.07]; p = 0.033). The all-cause death rate was also significantly lower in the ECMO application without or before CPR group. A comparison of the ECMO application without or before CPR group and no ECMO application group during the whole follow-up period revealed no significant differences in MACEs (Fig. 2, Table 3).

Independent predictors of the primary and secondary outcomes were identified using a multivariable Cox proportional hazard model. ECMO application was a significant and positive independent predictor of MACEs (HR 2.49 [95% CI 1.74–3.56]; p < 0.001) and all-cause death (HR 2.81 [95% CI 1.91–4.14]; p < 0.001) at 3 years (Table 4). CPR was also associated with a higher incidence of MACEs (HR 1.87 [95% CI 1.45–2.41]; p < 0.001) and all-cause death (HR 2.50 [95% CI 1.84–3.40]; p < 0.001). Age > 75 years, sex, serum creatinine level ≥ 2 mg/dL, left ventricular ejection fraction < 40%, sepsis, and multi-organ failure were also identified as independent predictors of MACEs (**Suppl. Table 1**).

Discussion

Herein, we compared 3-year clinical outcomes between the no ECMO application group and the ECMO application group with AMI complicated by cardiogenic shock. We found that the no ECMO application group showed significantly lower risks of all-cause death, cardiac death, and MACEs than the ECMO application group, which were consistently observed after multivariable analysis. Second, the ECMO application without or before CPR group showed significantly lower risks of all-cause death and MACEs than the ECMO application after CPR group, which were also consistently observed after multivariable analysis. Third, the ECMO application without or before CPR group showed similar outcomes of MACEs during a 3-year follow-up compared with the no ECMO application group.

Cardiogenic shock occurs in 5–10% of patients with AMI, and it is the leading cause of death after AMI [12]. The most common cause of AMI complicated by cardiogenic shock was predominant left ventricular failure (78.5%). Acute severe mitral regurgitation, ventricular septal rupture, and isolated right ventricular shock can also cause cardiogenic shock [13]. In the SHOCK trial, early revascularization showed a lower mortality rate at 6 months than medical treatment in patients with AMI complicated by cardiogenic shock due to left ventricular failure [2]. Consequently, the rate of PCI in cardiogenic shock continued to increase, and the mortality rate decreased accordingly. In the study by De Luca et al. [14], PCI in patients with AMI complicated by cardiogenic shock increased from 19% in 2001 to 60% in 2014, and accompanying in-hospital mortality decreased from 68% in 2001 to 38% in 2014. However, the clinical outcomes, including in-hospital mortality of AMI complicated by cardiogenic shock, remained high.

To overcome this problem, a mechanical circulatory support device can be considered. Venous arterial ECMO is a mechanical circulatory support device that draws blood from the venous system and passes it through a centrifugal pump, and then returns oxygenated blood to the arterial system [15, 16]. Consequently, venous arterial ECMO plays a role in earning time for myocardial recovery (bridge to recovery) or stabilizing the patient's condition before the consideration of further strategies (bridge to bridge or bridge to transplant) [17]. Several studies support venous arterial ECMO application in patients with cardiac arrest. In the study by Chen et al. [3], extracorporeal CPR was compared with conventional CPR in patients with in-hospital cardiac arrest of cardiac origin, who underwent CPR for > 10 min. The extracorporeal CPR group showed long-term survival benefits over the conventional CPR group at

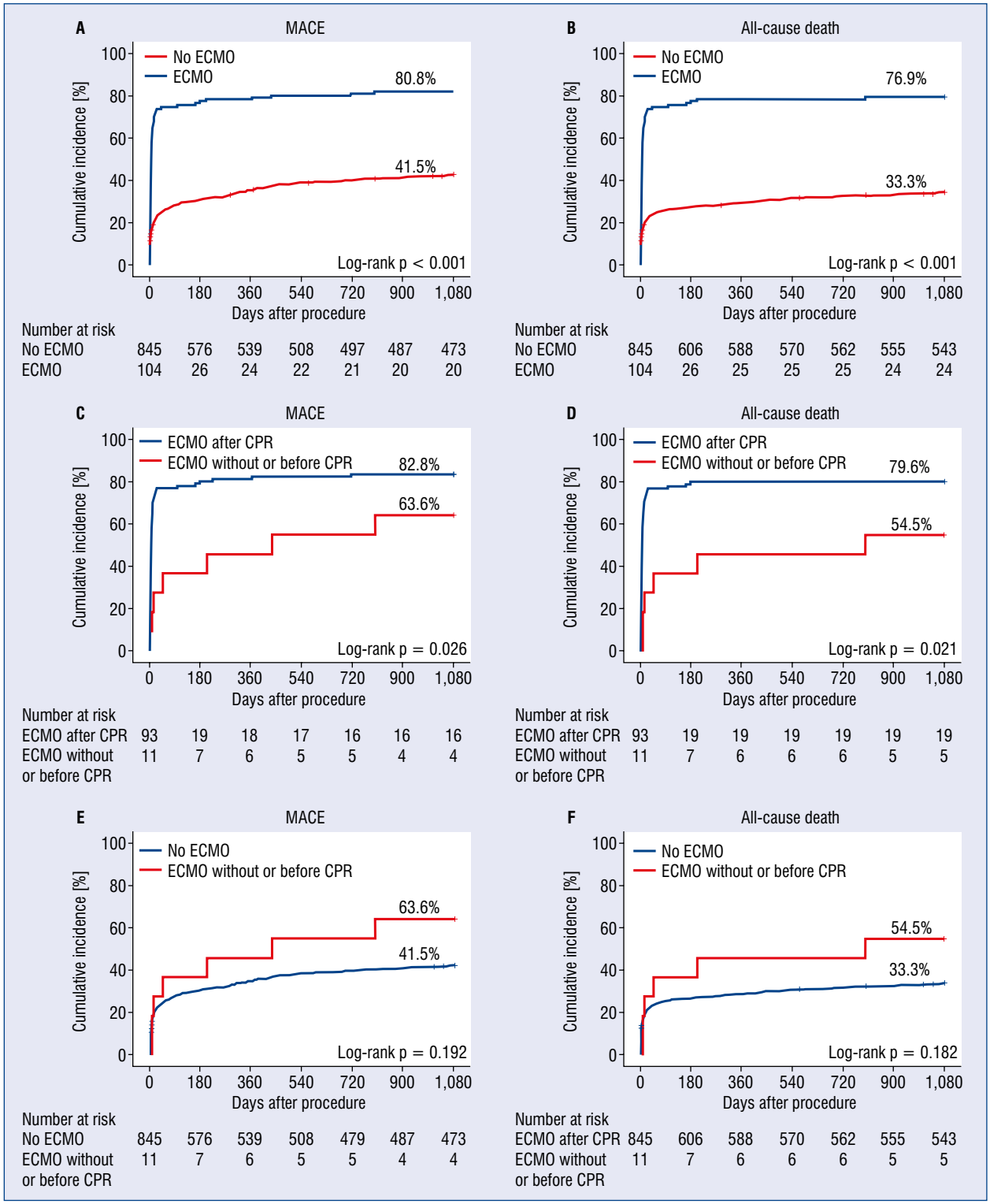


Figure 2. Cumulative incidence of major adverse cardiac events (MACE) and all-cause death in the no extracorporeal membrane oxygenation (ECMO) versus ECMO groups, the ECMO without or before cardiopulmonary resuscitation (CPR) versus ECMO after CPR groups, and the no ECMO versus ECMO without or before CPR groups. Kaplan-Meier estimate of the composite endpoint of MACE and all-cause death among the no ECMO and ECMO groups (**A**, **B**), the ECMO without or before CPR and ECMO after CPR groups (**C**, **D**), and the no ECMO and ECMO without or before CPR groups (**E**, **F**). P-values are calculated with the log rank test.

Table 3. Comparison of 3-year clinical outcomes according to extracorporeal membrane oxygenation (ECMO) application and ECMO application timing.

	No ECMO (n = 845)	ECMO (n = 104)	Unadjusted		Multivariable-adjusted	
			HR (95% CI)	P	HR (95% CI)	P
3-year follow-up						
All-cause death	281 (33.3)	80 (76.9)	3.72 (2.89–4.79)	< 0.001	2.81 (1.91-4.14)	< 0.001
Cardiac death	218 (25.8)	73 (70.2)	4.08 (3.12–5.34)	< 0.001	2.81 (1.84-4.30)	< 0.001
Spontaneous MI	24 (2.8)	1 (1.0)	0.91 (0.12–6.70)	0.923	0.96 (0.11–8.62)	0.973
Repeat revascularization	71 (8.4)	4 (3.8)	1.25 (0.46–3.41)	0.668	1.47 (0.49–4.46)	0.496
All-cause death or MI	298 (35.3)	81 (77.9)	3.62 (2.82–4.65)	< 0.001	2.76 (1.89–4.03)	< 0.001
MACE	351 (41.5)	84 (80.8)	3.36 (2.64–4.28)	< 0.001	2.49 (1.74–3.56)	< 0.001
	ECMO without or before CPR (n = 11)	**ECMO after CPR (n = 93)**	**Unadjusted**		**Multivariable-adjusted**	
			HR (95% CI)	P	HR (95% CI)	P
3-year follow-up						
All-cause death	6 (54.5)	74 (79.6)	2.55 (1.11–5.88)	0.028	4.79 (1.42–16.13)	0.011
Cardiac death	6 (54.5)	67 (72.0)	2.26 (0.98–5.23)	0.057	2.94 (0.95–9.16)	0.062
All-cause death or MI	7 (63.6)	74 (79.6)	2.19 (1.00–4.77)	0.049	8.074 (2.08–31.29)	0.003
MACE	7 (63.6)	77 (82.8)	2.33 (1.07–5.07)	0.033	5.94 (1.73–20.38)	0.005
	No ECMO (n = 845)	**ECMO without or before CPR (n = 11)**	**Unadjusted**		**Multivariable-adjusted**	
			HR (95% CI)	P	HR (95% CI)	P
3-year follow-up						
All-cause death	281 (33.3)	6 (54.5)	1.71 (0.76–3.84)	0.193	2.68 (1.05–6.81)	0.039
Cardiac death	218 (25.8)	6 (54.5)	2.17 (0.96–4.87)	0.062	3.62 (1.38–9.54)	0.009
Spontaneous MI	24 (2.8)	1 (9.1)	3.91 (0.53–28.93)	0.182	4.94 (0.66–36.85)	0.119
Repeat revascularization	71 (8.4)	1 (9.1)	1.28 (0.18–9.22)	0.806	1.19 (0.13–11.42)	0.878
All-cause death or MI	298 (35.3)	7 (63.6)	1.92 (0.91–4.06)	0.088	2.95 (1.25–6.97)	0.013
MACE	351 (41.5)	7 (63.6)	1.63 (0.77–3.44)	0.201	2.28 (0.98–5.31)	0.055

Values are number (%) unless otherwise indicated. The cumulative incidences of clinical outcomes are presented as Kaplan-Meier estimates during a median follow-up of 679 days. A multivariable Cox proportional hazard regression model was used to adjust for baseline differences between comparative groups; CI — confidence interval; CPR — cardiopulmonary resuscitation; ECMO — extracorporeal membrane oxygenation; HR — hazard ratio; MACE — major adverse cardiac event; MI — myocardial infarction

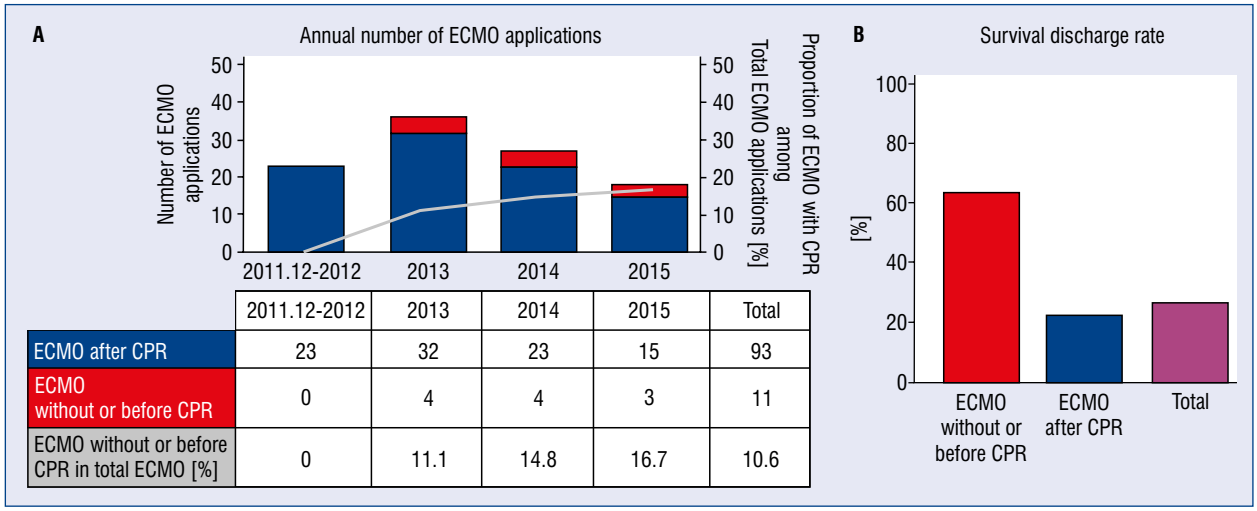
the 1-year follow-up (HR 0.51; 95% CI 0.35–0.74; p < 0.001) [3]. In the study by Shin et al. [18], the extracorporeal CPR group showed higher survival rates with minimal neurologic impairments than the conventional CPR group in patients with in-hospital cardiac arrest (HR 0.17; 95% CI 0.04–0.68; p = 0.012). The 2020 European Society of Cardiology guidelines also recommend short-term mechanical circulatory support application in patients with AMI complicated by cardiogenic shock as Class IIb and Level C, depending on the patient's characteristics such as age, underlying disease, neurological state, and long-term life expectancy [1]. However, few studies have reported on the optimal timing of ECMO application, and long-term clinical outcomes after ECMO application in patients with AMI complicated by cardiogenic shock.

In this study, 7.2% (n = 949) of patients with AMI complicated by cardiogenic shock among 13,104 patients with AMI underwent successful PCI. ECMO was applied in 11% (n = 104) of the enrolled patients with AMI complicated by cardiogenic shock, and ECMO without or before CPR was applied in only 10.6% (n = 11). Survival rates on discharge were 63.6% in the ECMO without or before CPR group, 22.6% in the ECMO after CPR group, and 26.9% in the total ECMO group (Fig. 3). In the study by Vallabhajosyula et al. [19], ECMO use with AMI in the United States increased 11.4--fold from 2000 to 2014. During this period, ECMO

Table 4. Independent predictors of clinical outcomes at 3 years.

	Hazard ratio	95% CI	P
All-cause death			
Age > 75 years	3.30	2.45–4.43	< 0.001
Sex	1.44	1.07–1.95	0.017
Diabetes mellitus	1.37	1.03–1.83	0.030
Creatinine ≥ 2 mg/dL	2.13	1.47–3.09	< 0.001
LVEF < 40%	2.04	1.53–2.72	< 0.001
Sepsis	1.86	1.13–3.07	0.015
Multi-organ failure	3.15	1.95–5.10	< 0.001
CPR	2.50	1.84–3.40	< 0.001
ECMO	2.81	1.91–4.14	< 0.001
MACE			
Age > 75 years	2.30	1.78–2.97	< 0.001
Sex	1.33	1.02–1.73	0.034
Creatinine ≥ 2 mg/dL	2.10	1.50–2.94	< 0.001
LVEF < 40%	1.65	1.28–2.12	< 0.001
Sepsis	1.81	1.13–2.89	0.013
MOF	3.39	2.12–5.42	< 0.001
CPR	1.87	1.45–2.41	< 0.001
ECMO	2.49	1.74–3.56	< 0.001

Hazard ratios and their 95% confidence intervals (CI) are calculated using multivariable Cox regression analysis. CPR — cardiopulmonary resuscitation; ECMO — extracorporeal membrane oxygenation; LVEF — left ventricular ejection fraction; MACE — major adverse cardiac event



	2011.12-2012	2013	2014	2015	Total
ECMO after CPR	23	32	23	15	93
ECMO without or before CPR	0	4	4	3	11
ECMO without or before CPR in total ECMO [%]	0	11.1	14.8	16.7	10.6

Figure 3. Number of extracorporeal membrane oxygenation (ECMO) applications performed during the study enrollment periods, and survival discharge rates in the ECMO without or before cardiopulmonary resuscitation (CPR) versus ECMO after CPR groups in acute myocardial infarction (AMI) complicated by cardiogenic shock. Although the proportion of ECMO applications without or before CPR among the total number of patients with an ECMO application tended to increase, it was still below 17% in 2015 (**A**). ECMO without or before CPR revealed a much higher survival discharge rate compared with ECMO after CPR (**B**).

was used in approximately 0.5% of patients with AMI complicated by cardiogenic shock. Moreover, the average survival rate on discharge for those treated with ECMO was 40.8%, which had increased from 0% in 2000 to 54.9% in 2014. The rate of ECMO application is higher in patients with AMI complicated by cardiogenic shock in South Korea compared with the United States and other countries [20]. However, there are several limitations to comparing the results directly. First, the enrollment period was different between the two studies. ECMO application also changed rapidly. Second, mechanical circulatory support devices such as Impella® had not yet been introduced; thus, the tendency was to rely on ECMO to treat cardiogenic shock in South Korea. Third, the Korean Acute Myocardial Infarction Registry – National Institutes of Health data includes only patients with AMI who underwent PCI in large-scale hospitals. All patients with AMI were included based on the Healthcare Quality and Utilization Project National Inpatient Sample data in the United States.

Another specific finding of this study was that the mortality rate of the total ECMO group and ECMO after CPR group were significantly higher in South Korea compared with the United States and other studies. In a systematic review, the survival rate on discharge ranged from 30% to 79.2% in patients with AMI complicated by cardiogenic shock who underwent ECMO application [21–26]. In the Extracorporeal Life Organization registry, the survival rate on discharge was approximately 42% in patients with refractory cardiogenic shock treated with venous arterial ECMO [27]. In our study, the ECMO application group had more negative factors in their baseline characteristics and procedural characteristics than the no ECMO application group. Moreover, the rate of ECMO application without or before CPR was considerably smaller than the rate of ECMO application after CPR. These results suggest that ECMO tended to be applied later for patients in poor condition. Several studies support the benefit of early ECMO application. In the study by Sheu et al. [4], early ECMO-assisted primary PCI was compared with conventional primary PCI in patients with ST-segment elevation myocardial infarction complicated by profound cardiogenic shock. The early ECMO-assisted primary PCI group showed a lower mortality rate than the conventional primary PCI group at the 30-day follow-up (HR 0.223; 95% CI 0.062–0.801; p = 0.021). In the study by Choi et al. [28], the early ECMO application before revascularization group showed a lower risk of composite in-hospital mortality, left ventricular assist device implantation, and heart transplantation than the ECMO application after revascularization group (HR 0.360; 95% CI 0.152–0.853; p = 0.020) or the E-CPR before revascularization group in patients with AMI complicated by cardiogenic shock. Although there are many reasons for hesitating or not using ECMO, such as age, underlying disease, economic conditions, and psychological resistance due to expected complications and prognosis after ECMO application, it is necessary to consider earlier ECMO application, especially before a CPR situation, based on these studies.

Limitations of the study

This study has several limitations. First, selection bias should be considered because the medical treatments and procedure strategies, including ECMO application, were performed based on individual physicians' decisions. Thus, multivariable analysis was performed to minimize selection bias. Second, although the date on which the event (CPR and ECMO application) occurred was recorded, the exact time (hour and minute) and duration were not recorded. Specific CPR data (location and presence or absence of early CPR) and the ECMO application method (cannulation techniques and with/without left ventricular unloading) were also not recorded. If CPR and ECMO application took place on the same day, the patient was classified as having undergone ECMO application after CPR. However, this assumption is acceptable because CPR is generally not performed after ECMO application. Third, the ECMO groups (especially ECMO without CPR) were relatively small. Further analysis will be needed by extending the research period to confirm the clinical effect of early ECMO application in patients with AMI complicated by cardiogenic shock. Furthermore, large-scale randomized controlled trials should be conducted to the extent that they would not pose an ethical or legal issue, such as in Society for Cardiovascular Angiography and Interventions stage B or C [29]. Fourth, lactate levels during hospitalization could not be checked in this registry, although these are part of the definition criteria for cardiogenic shock and robust tools for ECMO implantation and prognosis. Fifth, there are no data about left ventricular assist devices and heart transplantation, which can affect long-term clinical outcomes in patients with cardiogenic shock.

Conclusions

To date, ECMO has been used as salvage therapy for rescue, and it has not been used fre-

quently before the patient's condition has worsened. Herein, ECMO application without or before CPR showed good long-term clinical outcomes. Therefore, early application of ECMO can be considered a reasonable procedural strategy in patients with AMI complicated by cardiogenic shock, to improve clinical outcomes.

Acknowledgments

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Conflict of interest: None declared

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