ORIGINAL ARTICLE

Extracorporeal Life Support in Infarct-Related Cardiogenic Shock

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ABSTRACT

BACKGROUND

Extracorporeal life support (ECLS) is increasingly used in the treatment of infarct-related cardiogenic shock despite a lack of evidence regarding its effect on mortality.

METHODS

In this multicenter trial, patients with acute myocardial infarction complicated by cardiogenic shock for whom early revascularization was planned were randomly assigned to receive early ECLS plus usual medical treatment (ECLS group) or usual medical treatment alone (control group). The primary outcome was death from any cause at 30 days. Safety outcomes included bleeding, stroke, and peripheral vascular complications warranting interventional or surgical therapy.

RESULTS

A total of 420 patients underwent randomization, and 417 patients were included in final analyses. At 30 days, death from any cause had occurred in 100 of 209 patients (47.8%) in the ECLS group and in 102 of 208 patients (49.0%) in the control group (relative risk, 0.98; 95% confidence interval [CI], 0.80 to 1.19; P=0.81). The median duration of mechanical ventilation was 7 days (interquartile range, 4 to 12) in the ECLS group and 5 days (interquartile range, 3 to 9) in the control group (median difference, 1 day; 95% CI, 0 to 2). The safety outcome consisting of moderate or severe bleeding occurred in 23.4% of the patients in the ECLS group and in 9.6% of those in the control group (relative risk, 2.44; 95% CI, 1.50 to 3.95); peripheral vascular complications warranting intervention occurred in 11.0% and 3.8%, respectively (relative risk, 2.86; 95% CI, 1.31 to 6.25).

CONCLUSIONS

In patients with acute myocardial infarction complicated by cardiogenic shock with planned early revascularization, the risk of death from any cause at the 30-day follow-up was not lower among the patients who received ECLS therapy than among those who received medical therapy alone. (Funded by the Else Kröner Fresenius Foundation and others; ECLS-SHOCK ClinicalTrials.gov number, NCT03637205.)

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Cardiogenic shock develops in up to 10% of hospitalized patients with acute myocardial infarction and is the leading cause of death among these patients.[1] Treatment is limited to immediate revascularization of the culprit lesion to improve outcomes.[2-4] However, mortality remains high, with percentages of 40 to 50% within 30 days.[1]

Ongoing efforts to improve outcomes have led to an increase in the use of active mechanical circulatory support to achieve hemodynamic stabilization in severe shock. In particular, the frequency of the use of venoarterial extracorporeal membrane oxygenation, also called extracorporeal life support (ECLS), has risen by a factor of more than 10 during the past 10 years.[5] ECLS enables full circulatory and respiratory support, a feature that differentiates it from other bypass techniques. Its use has been facilitated by the development of smaller and easier-to-use systems, as well as techniques for nonsurgical percutaneous cannulation and vascular closure.

However, available evidence for the use of ECLS in cardiogenic shock resulting from acute myocardial infarction has been restricted to observational studies and three small randomized trials.[6-9] Potential benefits of hemodynamic support may be outweighed by a considerable risk of device-associated local and systemic complications, which include bleeding, stroke, limb ischemia, and hemolysis. We performed the ECLS-SHOCK trial to test the hypothesis that early routine ECLS treatment as compared with usual medical therapy alone would result in improved survival in patients with acute myocardial infarction complicated by cardiogenic shock for whom early revascularization was planned.

Methods

Trial Design and Oversight

We conducted this investigator-initiated, randomized, multicenter, open-label trial in two European countries (Germany and Slovenia). The primary objective was to determine whether patients with acute myocardial infarction complicated by cardiogenic shock (defined as stage C, D, or E of the Society for Cardiovascular Angiography and Interventions [SCAI] criteria)[10] with planned revascularization would benefit from early, unselective ECLS in addition to usual medical therapy as compared with usual medical therapy alone. The design of the trial has been published previously.[11] The trial was supported by the Else Kröner Fresenius Foundation, the German Heart Research Foundation, and the Helios Health Institute (formerly Leipzig Heart Institute).

The trial protocol (available with the full text of this article at NEJM.org) was approved by the ethics committee at each participating site. The trial was designed by the first author and was further modified by the steering committee. A data and safety monitoring board reviewed the safety aspects of the trial, and a clinical-events committee evaluated clinical end points. The first two and last two authors wrote the first draft of the manuscript. After modification by the other authors, all agreed to submit the manuscript for publication. The steering committee vouches for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Patients

Patients between 18 and 80 years of age with acute myocardial infarction complicated by cardiogenic shock and planned early revascularization by either percutaneous coronary intervention (PCI) or coronary-artery bypass grafting (CABG) were eligible for inclusion. Cardiogenic shock was defined as a systolic blood pressure of less than 90 mm Hg for more than 30 minutes or the initiation of catecholamines to maintain a systolic pressure of more than 90 mm Hg, an arterial lactate level of more than 3 mmol per liter, and signs of impaired organ perfusion with at least one of the following criteria: altered mental status, cold or clammy skin and limbs, or urine output of less than 30 ml per hour.

Excluded from the trial were patients who had undergone cardiopulmonary resuscitation for more than 45 minutes before randomization or who had a mechanical cause of cardiogenic shock or severe peripheral-artery disease precluding the insertion of ECLS cannulae. Detailed inclusion and exclusion criteria and a precise description of the stepwise informed consent process are provided in the Supplementary Appendix, available at NEJM.org.

Randomization and Treatment

Immediately after the performance of coronary angiography examining the coronary anatomy in patients for whom revascularization was planned, randomization was performed by means of a

Web-based system with the use of randomly changing blocks and stratification according to the trial site. Patients were assigned in a 1:1 ratio to receive either ECLS implantation plus usual medical therapy or usual medical therapy alone. PCI was the preferred revascularization strategy, although in patients who were unsuitable candidates for PCI, immediate CABG could be performed.[3,4]

In the ECLS group, ECLS was initiated during the index catheterization, preferably before PCI. The use of an antegrade arterial femoral sheath was strongly recommended to reduce the risk of lower limb ischemia. Details regarding ECLS treatment in the intensive care unit (ICU) and predefined criteria for left ventricular unloading, weaning, and removal are provided in the Supplementary Appendix.

Recommended treatment in the ICU was performed according to current guidelines.[12,13] In the control group, crossover to ECLS was to be avoided according to the trial protocol. However, in case of specific predefined criteria for hemodynamic deterioration under medical therapy, escalation therapy using other devices such as an intraaortic balloon pump or a microaxial transvalvular flow pump was allowed. These criteria included severe hemodynamic instability with impending hemodynamic collapse, an increase in the arterial lactate level of more than 3 mmol per liter during a 6-hour period, or an increase in vasopressor use by 50% from baseline to maintain a mean arterial blood pressure of more than 65 mm Hg.

PRIMARY AND SECONDARY OUTCOMES

The primary outcome was death from any cause at 30 days. Key secondary outcomes were the time until hemodynamic stabilization, the length of ICU stay, acute renal failure warranting renal-replacement therapy, recurrent myocardial infarction, and rehospitalization for congestive heart failure. Other secondary outcomes included the initiation and duration of catecholamine therapy and the use and duration of mechanical ventilation, along with a poor neurologic outcome (defined post hoc as a Cerebral Performance Category [CPC] score of 3 or 4) at 30 days. (The CPC ranges from 1 to 5, with scores of 3, 4, and 5 suggesting a poor outcome [severe neurologic disability, persistent vegetative state, or brain death]). For the assessment of renal and myocardial injury, serial measurements of the estimated creatinine clearance and high-sensitivity cardiac troponin level were obtained. Disease severity was determined by arterial lactate levels and serial assessment of the Simplified Acute Physiology Score II (SAPS II), which measures the severity of disease with scores ranging from 0 (best) to 163 (worst).

Safety outcomes were defined as moderate or severe bleeding (type 3 to 5 according to the Bleeding Academic Research Consortium [BARC] criteria), stroke or systemic embolization, and peripheral ischemic vascular complications warranting surgical or interventional therapy. Details regarding definitions and reporting of outcomes are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

We based the sample-size calculation on an estimated mortality of 35% in the ECLS group and 49% in the control group using nQuery Advisor 7.0 (Statistical Solutions) (see the Supplementary Appendix). The trial was designed with two-sided alternatives and one interim analysis after completion of the 30-day follow-up of 50% of the patients. On the basis of a global type I error of 0.05, we calculated that the enrollment of 394 patients would provide a power of 80% to rule out the null hypothesis of no difference between the two treatment groups at a two-sided alpha level of 0.048 for the final analysis. In accordance with an estimated 6% withdrawal, a total of 420 patients were recruited.

The primary analysis was performed according to the intention-to-treat principle. Sensitivity analyses were performed in the per-protocol and as-treated populations for evaluation of data robustness. We used the chi-square test to compare the incidence of a primary-outcome event and calculated the relative risk with the corresponding 95% confidence interval. We also calculated Kaplan–Meier curves to visualize the cumulative events in the two trial groups during the 30-day follow-up period.

Effect sizes regarding secondary outcomes are presented as relative risks or Hodges–Lehmann estimators with corresponding 95% confidence intervals calculated as appropriate. Predefined subgroup analyses were performed with respect to sex, age (<65 years vs. ≥65 years), the presence or absence of diabetes, presence or absence of ST-segment elevation, anterior myocardial infarc-

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	ECLS (N=209)	Control (N=208)
Median age (IQR) — yr	62 (56–69)	63 (57–71)
Male sex — no. (%)	170 (81.3)	169 (81.2)
Median body-mass index (IQR)†	27 (25–30)	28 (25–31)
Cardiovascular risk factors — no./total no. (%)		
Current smoking	74/204 (36.3)	71/206 (34.5)
Hypertension	118/207 (57.0)	115/206 (55.8)
Hypercholesterolemia	55/207 (26.6)	74/206 (35.9)
Diabetes mellitus	70/208 (33.7)	60/206 (29.1)
Cardiovascular history — no./total no. (%)		
Myocardial infarction	23/208 (11.1)	31/206 (15.0)
PCI	27/208 (13.0)	43/206 (20.9)
CABG	5/208 (2.4)	6/207 (2.9)
Stroke	20/208 (9.6)	11/207 (5.3)
Peripheral-artery disease	21/208 (10.1)	16/206 (7.8)
Signs of impaired organ perfusion — no.(%)		
Altered mental status	200 (95.7)	198 (95.2)
Cold, clammy skin and limbs	202 (96.7)	204 (98.1)
Oliguria	150 (71.8)	150 (72.1)
Median blood pressure (IQR) — mm Hg		
Systolic	95 (80–120)	97 (80–120)
Diastolic	61 (50–73)	60 (50–71)
Median heart rate (IQR) — beats/min	90 (75–110)	95 (71–110)
ST-segment elevation myocardial infarction — no./total no. (%)	135/204 (66.2)	141/207 (68.1)
Fibrinolysis <24 hr before randomization — no./total no. (%)	6/208 (2.9)	9/208 (4.3)
Resuscitation before randomization — no. (%)	162 (77.5)	162 (77.9)
Median time until return of spontaneous circulation during longest continuous resuscitation (IQR) — min	20 (10–25)	20 (12–28)
No. of diseased vessels — no./total no. (%)		
1	71/203 (35.0)	63/200 (31.5)
2	71/203 (35.0)	53/200 (26.5)
3	61/203 (30.0)	84/200 (42.0)
Infarct-related artery — no./total no. (%)		
Left anterior descending	95/203 (46.8)	97/200 (48.5)
Left circumflex	36/203 (17.7)	35/200 (17.5)
Right coronary	52/203 (25.6)	48/200 (24.0)
Left main	20/203 (9.9)	20/200 (10.0)
Median left ventricular ejection fraction (IQR) — %	30 (20–35)	30 (20–40)
Laboratory values on admission		
Median pH (IQR)	7.2 (7.1–7.3)	7.2 (7.1–7.3)
Median lactate (IQR) — mmol/liter	6.8 (4.5–9.6)	6.9 (4.6–10.0)
Median creatinine (IQR) — mg/dl	1.2 (1.0–1.5)	1.3 (1.1–1.6)
Median high-sensitivity cardiac troponin T (IQR) — ng/liter	1540 (232–6630)	987 (173–5700)

Table 1. (Continued.)

Characteristic	ECLS (N = 209)	Control (N = 208)
SCAI shock stage — no. (%)‡		
C	104 (49.8)	111 (53.4)
D	38 (18.2)	18 (8.7)
E	67 (32.1)	79 (38.0)

* To convert the values for creatinine to micromoles per liter, multiply by 88.4. CABG denotes coronary-artery bypass grafting, ECLS extracorporeal life support, IQR interquartile range, and PCI percutaneous coronary intervention.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ At the start of the trial, the Society for Cardiovascular Angiography and Interventions (SCAI) shock stage was not available and also had not been adapted to include its current dynamic criteria for staging,[10] so a modified post hoc definition was used as follows: stage C, a lactate level of more than 3 mmol per liter at baseline with a lower-than-baseline lactate level at 8 hours; stage D, a lactate level of more than 3 mmol per liter at baseline with a higher-than-baseline lactate level at 8 hours or death within 8 hours; and stage E, a lactate level of more than 8 mmol per liter at baseline.

tion versus infarct at another location, and arterial lactate level (3 to 6 mmol per liter vs. >6 mmol per liter) on admission. In addition, a post hoc subgroup analysis of resuscitation versus no resuscitation before randomization was performed. A forest plot of the relative risk for the primary outcome and 95% confidence intervals resulting from univariate comparisons between the treatment groups was computed for these subgroups. The widths of all 95% confidence intervals have not been adjusted for multiplicity and may not be used in place of hypothesis testing. All statistical analyses were performed with the use of Statistical Analysis Software, version 9.4 (SAS Institute).

RESULTS

PATIENTS

From June 2019 through November 2022, a total of 877 patients were screened at 44 centers in Germany and Slovenia; 420 patients were subsequently enrolled in the trial (Fig. S1 in the Supplementary Appendix). After the exclusion of 3 patients (2 in the ECLS group and 1 in the control group) who did not provide consent, 209 patients in the ECLS group and 208 in the control group were included in the final analyses.

The characteristics of the patients were well balanced between the treatment groups at baseline (Table 1). The median age was 63 years (interquartile range, 56 to 70) with a predominance of men (81.3%). Two thirds of the patients presented with ST-segment elevation myocardial infarction, and the left anterior descending artery was the most common infarct site (in 47.6%). Approximately two thirds of the patients had multivessel coronary artery disease. A total of 77.7% of the patients underwent cardiopulmonary resuscitation before randomization. The median lactate level before revascularization was 6.9 mmol per liter (interquartile range, 4.6 to 9.9).

PROCEDURES AND TREATMENT

Procedural characteristics and details regarding treatment are provided in Table 2. Revascularization was performed by PCI in the majority of patients (96.6%). Details regarding anticoagulant and antiplatelet therapy during and after PCI as well as cardiovascular medication until discharge are provided in Tables S1 to S3.

In the ECLS group, ECLS treatment was initiated during the index angiography in 192 patients (91.9%), with a balanced insertion rate before or during revascularization or after revascularization. ECLS was not initiated in 17 patients in the ECLS group (8.1%), including in 4 patients who died before initiation. ECLS was initiated in 26 patients in the control group (12.5%), including 22 patients within 24 hours after randomization and 4 patients thereafter. Reasons for crossovers are provided in the Supplementary Appendix.

The median duration of ECLS therapy in the ECLS group was 2.7 days (interquartile range, 1.5 to 4.8). Implementation of at least one left ventricular unloading strategy was reported in 5.8% of the patients in the ECLS group (Table S4).

The overall need for catecholamine therapy

Table 2. Treatment.*

Characteristic	ECLS (N=209)	Control (N=208)
Catheterization access — no./total no. (%)		
Femoral	156/208 (75.0)	148/207 (71.5)
Radial	52/208 (25.0)	59/207 (28.5)
Type of revascularization — no./total no. (%)		
PCI	199/208 (95.7)	199/204 (97.5)
CABG	1/208 (0.5)	0/204
PCI with transfer to CABG	2/208 (1.0)	0/204
No revascularization	6/208 (2.9)	5/204 (2.5)
TIMI grade for blood flow of culprit lesion — no./total no. (%)		
Before revascularization		
0	96/202 (47.5)	105/197 (53.3)
I	41/202 (20.3)	33/197 (16.8)
II	40/202 (19.8)	40/197 (20.3)
III	25/202 (12.4)	19/197 (9.6)
After revascularization		
0	2/192 (1.0)	0/189
I	6/192 (3.1)	0/189
II	10/192 (5.2)	12/189 (6.3)
III	174/192 (90.6)	177/189 (93.7)
Immediate PCI of nonculprit lesions — no./total no. (%)	50/203 (24.6)	42/200 (21.0)
ECLS therapy — no. (%)	192 (91.9)	26 (12.5)
Initiation in catheterization laboratory		
Before revascularization	42/192 (21.9)	4/26 (15.4)
During revascularization	50/192 (26.0)	8/26 (30.8)
After revascularization	100/192 (52.1)	7/26 (26.9)
Initiation after catheterization laboratory		
<24 hr	0/192	3/26 (11.5)
≥24 hr	0/192	4/26 (15.4)
Median duration of ECLS therapy (IQR) — days	2.7 (1.5–4.8)	2.7 (2.2–3.8)
Peripheral antegrade perfusion sheath during ECLS therapy — no./total no. (%)	183/192 (95.3)	16/19 (84.2)
Median diameter of arterial cannula (IQR) — French size	17 (15–18)	17 (15–17)
Active left ventricular unloading during ECLS therapy — no./total no. (%)	11/191 (5.8)	6/19 (31.6)
Other mechanical circulatory support in patients without ECLS — no./total no. (%)	0/17	28/182 (15.4)
Intraaortic balloon pump	—	1/28 (3.6)
Impella 2.5	—	1/28 (3.6)
Impella CP	—	24/28 (85.7)
Impella 5.0	—	1/28 (3.6)
Impella 5.5	—	1/28 (3.6)
Permanent left ventricular assist device — no./total no. (%)	1 (0.5)	1 (0.5)

Table 2. (Continued.)

Characteristic	ECLS (N=209)	Control (N=208)
Target temperature management — no./total no. (%)	82/209 (39.2)	109/208 (52.4)
Invasive mechanical ventilation		
Patients — no./total no. (%)	183/203 (90.1)	177/202 (87.6)
Median duration (IQR) — days	7.0 (4.0–12.0)	5.0 (3.0–9.0)
Catecholamine requirement — no./total no. (%)	203/209 (97.1)	195/208 (93.8)
Norepinephrine	181/203 (89.2)	181/195 (92.8)
Epinephrine	63/203 (31.0)	69/195 (35.4)
Dobutamine	88/203 (43.3)	59/195 (30.3)
Dopamine	1/203 (0.5)	0/195
Sepsis within 30 days after randomization — no. (%)	21 (10.0)	21 (10.1)

* TIMI denotes Thrombolysis in Myocardial Infarction.

was well balanced between the groups. Dobutamine was more frequently administered in the ECLS group.

A total of 28 patients (15.4%) in the control group received mechanical circulatory support other than ECLS, primarily with the use of a microaxial transvalvular device. Of these patients, 2 did not fulfill the predefined escalation criteria for the use of mechanical circulatory support (see the Supplementary Appendix).

PRIMARY AND SECONDARY OUTCOMES

Death from any cause at 30 days (the primary outcome) occurred in 100 of 209 patients (47.8%) in the ECLS group and in 102 of 208 patients (49.0%) in the control group (relative risk, 0.98; 95% confidence interval [CI], 0.80 to 1.19; P=0.81) (Table 3 and Fig. 1). The results of sensitivity analyses in the per-protocol and as-treated populations were similar to the findings in the primary analysis (Fig. S2). Details with respect to causes of death are provided in Table S5.

Prespecified and post hoc analyses showed results across all subgroups that were consistent with those in the primary analysis (Fig. 2). An additional post hoc analysis showed similar mortality results regardless of the number of patients who had been enrolled at each center, with an incidence of death of 50.9% in centers that enrolled fewer than 5 patients and 48.1% in those that enrolled 5 patients or more (relative risk, 1.02; 95% CI, 0.94 to 1.09).

No material difference was observed between treatment groups regarding the duration of catecholamine therapy and the time until hemodynamic stabilization. Durations of mechanical ventilation and intensive care treatment are provided in Table 2. The frequencies of renal-replacement therapy, repeat revascularization, myocardial reinfarction, rehospitalization for congestive heart failure within 30 days, and poor neurologic outcome at 30 days are provided in Table 3. Results for peak troponin levels as well as serial assessments of the SAPS II score, lactate level, and glomerular filtration rate are shown in Figures S3 through S6.

SAFETY

Moderate or severe bleeding occurred in 23.4% of the patients in the ECLS group and in 9.6% of those in the control group (relative risk, 2.44; 95% CI, 1.50 to 3.95); peripheral vascular complications warranting intervention occurred in 11.0% and 3.8%, respectively (relative risk, 2.86; 95% CI, 1.31 to 6.25). The frequency of stroke or systemic embolization was 3.8% in the ECLS group and 2.9% in the control group (relative risk, 1.33; 95% CI, 0.47 to 3.76) (Table 3).

DISCUSSION

In our multicenter, randomized trial, we found that early routine ECLS was not superior to usual medical therapy alone with respect to death from any cause at 30 days in patients with acute myocardial infarction complicated by cardiogenic shock for whom early revascularization was planned. ECLS was associated with more com-

Table 3. Clinical Outcomes at 30 Days.

Outcome	ECLS (N=209)	Control (N=208)	Effect Size (95% CI)*
Primary outcome			
Death from any cause — no. (%)	100 (47.8)	102 (49.0)	Relative risk, 0.98 (0.80 to 1.19)
Secondary outcomes			
Renal-replacement therapy — no. (%)	17 (8.1)	29 (13.9)	Relative risk, 0.58 (0.33 to 1.03)
Repeat revascularization — no. (%)	18 (8.6)	22 (10.6)	Relative risk, 0.81 (0.45 to 1.47)
Myocardial reinfarction — no. (%)	2 (1.0)	2 (1.0)	Relative risk, 1.00 (0.07 to 12.72)†
Rehospitalization for congestive heart failure — no. (%)	3 (1.4)	2 (1.0)	Relative risk, 1.49 (0.24 to 13.61)†
Poor neurologic outcome, CPC 3 or 4 — no./total no. (%)‡	27/109 (24.8)	24/106 (22.6)	Relative risk, 1.03 (0.88 to 1.19)
Median duration of invasive mechanical ventilation (IQR) — days	7.0 (4.0 to 12.0)	5.0 (3.0 to 9.0)	HLE, 1 (0 to 2)
Median time until hemodynamic stabilization (IQR) — days	3.1 (1.2 to 6.6)	3.1 (1.2 to 5.4)	HLE, 0.27 (–0.41 to 1.14)
Median duration of catecholamine therapy (IQR) — days	5.0 (2.5 to 8.0)	4.0 (2.0 to 7.0)	HLE, 1 (0 to 1)
Median duration of intensive care treatment (IQR) — days	10.0 (4.0 to 16.0)	8.0 (4.0 to 13.0)	HLE, 1 (0 to 3)
Median duration of hospital stay (IQR) — days	12.0 (5.0 to 20.0)	10.0 (3.0 to 19.0)	HLE, 2 (0 to 4)
Safety outcomes			
Peripheral ischemic vascular complications warranting surgical or interventional therapy — no. (%)	23 (11.0)	8 (3.8)	Relative risk, 2.86 (1.31 to 6.25)
Stroke or systemic embolization — no. (%)	8 (3.8)	6 (2.9)	Relative risk, 1.33 (0.47 to 3.76)
Moderate or severe bleeding — no. (%)§	49 (23.4)	20 (9.6)	Relative risk, 2.44 (1.50 to 3.95)

* The Hodges–Lehmann estimator (HLE) was used to calculate the median of differences between the patients in the ECLS group and those in the control group. The widths of the 95% confidence intervals were not adjusted for multiplicity and may not be used in place of hypothesis testing.
† Exact confidence intervals were calculated by means of Fisher's exact test.
‡ The Cerebral Performance Category (CPC) score evaluates neurologic outcome on a scale of 1 to 5. Scores of 3, 4, and 5 reflect a poor outcome (severe neurologic disability, persistent vegetative state, or brain death). The dichotomization to define a poor neurologic outcome as a CPC score of 3 or 4 was made post hoc, as detailed in the Supplementary Appendix.
§ Moderate or severe bleeding was defined as Bleeding Academic Research Consortium (BARC) types 3 to 5, which are detailed in the Supplementary Appendix.

plications, in particular bleeding and peripheral vascular events.

The attempt to achieve hemodynamic stabilization in patients with severe or rapidly deteriorating infarct-related cardiogenic shock is the most common indication for initiation of ECLS therapy.[12,13] The use of ECLS and other techniques for mechanical circulatory support increased substantially when percutaneous systems became widely available and after studies showed a lack of survival benefit for the intraaortic balloon pump as a former standard of hemodynamic support.[14,15] On the basis of findings from observational studies, current international guidelines and scientific statements support a strategy of mechanical circulatory support, albeit based on weak levels of evidence.[13,16]

Our trial aimed to include only patients with

more advanced cardiogenic shock (required lactate level, >3 mmol per liter) because such patients were thought to be the most likely to benefit from extracorporeal hemodynamic support.[10] Enrollment of these patients probably explains the overall increased mortality in the two trial groups as compared with previous trials involving a similar population.[2,4,15]

So far, three randomized trials that have evaluated the effect of ECLS in patients with cardiogenic shock have shown results in line with our findings. The first very small study showed no effect on left ventricular ejection fraction at 30 days in patients with infarct-related cardiogenic shock.[7] In the second and slightly larger trial involving 122 patients, investigators found no difference in a composite outcome consisting of death from any cause, circulatory arrest after resuscitation, or the use of a mechanical assist device including ECLS in patients with severe or deteriorating cardiogenic shock, regardless of whether acute myocardial infarction was the trigger, and no differences in mortality were observed.[6] The third trial was stopped early because of slow enrollment after only 35 of the planned 428 patients had undergone randomization, which precluded meaningful conclusions regarding mortality.[9]

Reasons for the absence of benefit of ECLS in cardiogenic shock could be multifactorial. First, the risk and associated device-related complications may counterbalance any potential benefit. In our trial, major bleeding episodes were considerably more frequent in the ECLS group than in the control group, and it is well known that bleeding has a major negative effect on the outcome in acute coronary syndromes and cardiogenic shock.[17] Also, peripheral ischemic complications warranting intervention occurred more often in the ECLS group than in the control group. The incidence of both major bleeding and peripheral ischemic complications was consistent with the incidence reported in the literature. Thus, despite ongoing efforts to reduce the risk of complications through such innovations as the use of smaller cannulae and a reduced need for anticoagulation, such complications will continue to be a clinically relevant problem.[18] A longer duration of mechanical ventilation as observed in the ECLS group in our trial could likewise alter outcomes.[19] Furthermore, peripheral ECLS insertion is associated with increased left ventricular afterload owing to retrograde aortic flow. Therefore, different left ventricular unloading strategies have been developed. Recent nonrandomized studies have indicated a potential benefit for concomitant unloading devices as compared with ECLS alone but have suggested higher frequencies of such complications as bleeding, hemolysis, and vascular complications.[20,21] In our trial, although established signs of progressive left ventricular failure were predefined in the protocol as an indication for left ventricular unloading, the unloading rate of 5.8% was relatively low as compared with rates in observational and small prospective studies.[22,23] Randomized trials are needed to evaluate whether unloading affects outcomes in ECLS treatment. A higher frequency of dobutamine use, as was observed in the ECLS group, potentially suggests an increase in the left ventricular afterload, which is additively associated with concerns about an increase in oxygen consumption and related adverse effects.[13]

Another possible reason for the lack of benefit of ECLS in our trial could be that patients had poor outcomes that were not primarily related to circulatory failure. As a result of the inclusion criteria, our trial aimed to include predominantly patients with SCAI shock stages C through

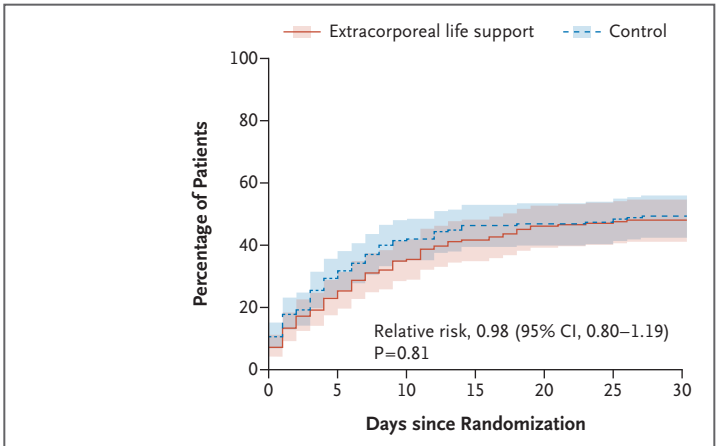

Figure 1. Death from Any Cause at 30 Days.

Shown are the time-to-event curves for death from any cause at 30 days (the primary outcome) among the patients who received extracorporeal life support plus medical therapy as compared with those who received only medical therapy (control). The shaded areas indicate the 95% confidence intervals.

E,[10] so more patients underwent cardiopulmonary resuscitation before randomization than in previous trials.[2,4,15] A high incidence of resuscitation with the competing risk of cerebral injury may diminish the possibility that ECLS positively influences prognosis. Debate is ongoing about whether to exclude patients who have undergone resuscitation from enrollment in randomized trials involving cardiogenic shock. However, such an exclusion would limit the generalizability of the trial results.[24] Patients who had undergone resuscitation had a survival (>50%) similar to those who had not undergone resuscitation, and subgroup analyses did not suggest differences in outcome between the two treatment groups. Refractory cardiogenic shock was the main cause of death in more than half the patients in both groups, whereas death after brain injury was reported in approximately one fourth. In the context of brain injuries, a lower frequency of target-temperature management was reported in the ECLS group than in the control group. However, because the ECLS system itself could have been used for temperature control or fever prevention, such measures in that group may have been underreported.

Our trial has several limitations. First, blinding of the intervention was not possible. This factor may have influenced the therapeutic decisions of treating physicians. Second, a total of 39 patients crossed over from their assigned group to the other group. In 7 patients, this crossover occurred after refractory cardiac arrest in the control group for which ECLS was the only available technique for restoring circulation. Thus, the use of ECLS in these situations was reasonable. Patients with cardiogenic shock after acute myocardial infarction are generally heterogeneous in terms of their clinical presentation and course. Therefore, ECLS might have been beneficial in certain subgroups only, even though there was no such signal in the prespecified and post hoc subgroup analyses. Finally, to allow for generalizability, centers with both medium and high volumes of ECLS use were in-

Subgroup	Death from Any Cause at 30 Days		Relative Risk (95%)
	Control	Extracorporeal Life Support	
	no. of patients with events/total no. of patients (%)		
Sex			
Male	79/169 (46.7)	78/170 (45.9)	0.98 (0.81–1.20)
Female	23/39 (59.0)	22/39 (56.4)	0.94 (0.56–1.58)
Age			
<65 yr	41/112 (36.6)	50/124 (40.3)	1.06 (0.87–1.30)
≥65 yr	61/96 (63.5)	50/85 (58.8)	0.88 (0.61–1.28)
Diabetes			
No	62/146 (42.5)	57/138 (41.3)	0.98 (0.80–1.19)
Yes	39/60 (65.0)	42/70 (60.0)	0.87 (0.56–1.37)
Type of infarction			
Non–ST-segment elevation myocardial infarction	36/66 (54.5)	37/69 (53.6)	0.98 (0.68–1.41)
ST-segment elevation myocardial infarction	65/141 (46.1)	59/135 (43.7)	0.96 (0.77–1.18)
ST-segment elevation myocardial infarction type			
Anterior infarction	39/85 (45.9)	33/75 (44.0)	0.97 (0.73–1.28)
Nonanterior infarction	26/56 (46.4)	25/59 (42.4)	0.93 (0.67–1.29)
Arterial lactate			
≤6 mmol/liter	24/85 (28.2)	30/87 (34.5)	1.09 (0.89–1.34)
>6 mmol/liter	75/120 (62.5)	69/120 (57.5)	0.88 (0.65–1.20)
CPR			
No	24/46 (52.2)	22/47 (46.8)	0.90 (0.60–1.35)
Yes	78/162 (48.1)	78/162 (48.1)	1.00 (0.81–1.23)

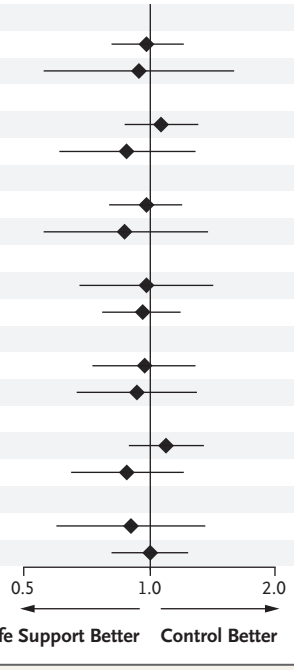

Figure 2. Subgroup Analysis of the Primary Outcome.

Shown is a forest plot of the relative risk of death from any cause at 30 days (the primary outcome) in prespecified subgroups and in one post hoc subgroup (cardiopulmonary resuscitation [CPR] before randomization). The widths of the confidence intervals were not adjusted for multiplicity and may not be used in place of hypothesis testing.

cluded. Theoretically, experience in device operation could influence outcomes. However, the current post hoc analysis of patient volumes according to center and observational data do not support an effect of patient volume on mortality among those receiving ECLS therapy.[25]

In patients with acute myocardial infarction complicated by cardiogenic shock and revascularization, the incidence of death from any cause at 30 days was not lower among patients receiving early unselective ECLS than among those receiving medical therapy alone.

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APPENDIX

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