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Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome

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ABSTRACT

BACKGROUND

The efficacy of venovenous extracorporeal membrane oxygenation (ECMO) in patients with severe acute respiratory distress syndrome (ARDS) remains controversial.

METHODS

In an international clinical trial, we randomly assigned patients with very severe ARDS, as indicated by one of three criteria — a ratio of partial pressure of arterial oxygen (Pao_2) to the fraction of inspired oxygen (Fio_2) of less than 50 mm Hg for more than 3 hours; a Pao_2:Fio_2 of less than 80 mm Hg for more than 6 hours; or an arterial blood pH of less than 7.25 with a partial pressure of arterial carbon dioxide of at least 60 mm Hg for more than 6 hours — to receive immediate venovenous ECMO (ECMO group) or continued conventional treatment (control group). Crossover to ECMO was possible for patients in the control group who had refractory hypoxemia. The primary end point was mortality at 60 days.

RESULTS

At 60 days, 44 of 124 patients (35%) in the ECMO group and 57 of 125 (46%) in the control group had died (relative risk, 0.76; 95% confidence interval [CI], 0.55 to 1.04; P=0.09). Crossover to ECMO occurred a mean (±SD) of 6.5±9.7 days after randomization in 35 patients (28%) in the control group, with 20 of these patients (57%) dying. The frequency of complications did not differ significantly between groups, except that there were more bleeding events leading to transfusion in the ECMO group than in the control group (in 46% vs. 28% of patients; absolute risk difference, 18 percentage points; 95% CI, 6 to 30) as well as more cases of severe thrombocytopenia (in 27% vs. 16%; absolute risk difference, 11 percentage points; 95% CI, 0 to 21) and fewer cases of ischemic stroke (in no patients vs. 5%; absolute risk difference, –5 percentage points; 95% CI, –10 to –2).

CONCLUSIONS

Among patients with very severe ARDS, 60-day mortality was not significantly lower with ECMO than with a strategy of conventional mechanical ventilation that included ECMO as rescue therapy. (Funded by the Direction de la Recherche Clinique et du Développement and the French Ministry of Health; EOLIA ClinicalTrials.gov number, NCT01470703.)

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The acute respiratory distress syndrome (ARDS) is associated with high mortality despite the use of low-volume, low-pressure ventilation strategies that are aimed at reducing ventilator-induced lung injury.[1,2] The most severe forms of ARDS may be associated with mortality exceeding 60%.[3-5] In these situations, some centers will use venovenous extracorporeal membrane oxygenation (ECMO).[6-9] There have been major advances in the past few years regarding the technology of ECMO circuits.[7] In this context, patients who received ECMO therapy during the influenza A (H1N1) pandemic in 2009 appeared to benefit, but the studies in which they were examined were not randomized.[10-12] Around the same time, a randomized trial that assigned patients with ARDS to an expert center for consideration of ECMO as part of a treatment protocol yielded promising results, although methodologic issues limited the conclusions that could be drawn from the trial.[13] We designed the ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) trial to determine the effect of early initiation of ECMO in patients with the most severe forms of ARDS.

Methods

Trial Design and Oversight

We conducted an international, randomized trial. Each local independent ethics review board approved the trial protocol, which is available with the full text of this article at NEJM.org. The trial was sponsored and conducted largely in France by the Direction de la Recherche Clinique et du Développement, Assistance Publique–Hôpitaux de Paris, with a grant from the French Ministry of Health. International centers that enrolled patients outside France were the legal sponsor for the trial in their own country. An independent data and safety monitoring committee periodically reviewed trial outcomes. The members of the writing committee wrote all drafts of the manuscript. All the authors approved the final version of the manuscript and made the decision to submit it for publication. They also verified the data and vouch for the completeness of the data, the accuracy of the analyses, and the fidelity of the trial to the protocol.

Maquet-Getinge provided HLS ECMO cannulas, the CardioHelp device, and circuits (HLS Set Advanced 7.0). Neither Maquet-Getinge nor the trial sponsors participated in the trial design; the data collection, analysis, or interpretation; or the writing or submission of the manuscript. Additional information is provided in the Supplementary Appendix, available at NEJM.org.

Patients

Patients were eligible for enrollment if their condition fulfilled the American–European Consensus Conference definition for ARDS,[14] if they had undergone endotracheal intubation and had been receiving ventilation for less than 7 days, and if they met disease-severity criteria as outlined in Section II.1 of the Supplementary Appendix (including a ratio of partial pressure of arterial oxygen [Pao_2] to the fraction of inspired oxygen [Fio_2] of <50 mm Hg for >3 hours, a Pao_2:Fio_2 of <80 mm Hg for >6 hours, or an arterial blood pH of <7.25 with a partial pressure of arterial carbon dioxide [$Paco_2$] of ≥60 mm Hg for >6 hours, with the respiratory rate increased to 35 breaths per minute and mechanical-ventilation settings adjusted to keep a plateau pressure of ≤32 cm of water) despite ventilator optimization (defined as a fraction of inspired oxygen [Fio_2] of ≥0.80, a tidal volume of 6 ml per kilogram of predicted body weight, and a positive end-expiratory pressure [PEEP] of ≥10 cm of water). Physicians were encouraged to use neuromuscular blocking agents and prone positioning before randomization. Other adjunctive therapies, such as inhaled nitric oxide, recruitment maneuvers (i.e., procedures that are used to reinflate collapsed lung units and that involve sustained application of an airway pressure of >35 cm of water),[2] high-frequency oscillatory ventilation, or almitrine infusion, were allowed at the discretion of the responsible clinicians.

Exclusion criteria were an age of less than 18 years; receipt of mechanical ventilation for 7 days or longer; pregnancy; a weight of more than 1 kg per centimeter of height or a body-mass index (the weight in kilograms divided by the square of the height in meters) of more than 45; long-term chronic respiratory insufficiency treated with oxygen therapy or noninvasive ventilation; cardiac failure resulting in venoarterial ECMO; a history of heparin-induced thrombocytopenia; cancer with a life expectancy of less than 5 years; a moribund condition or a Simplified Acute Physiology Score (SAPS-II) value of more than 90 (on a scale from 0 to 163, with higher scores indicating greater severity of illness) on the day of randomization; a current non–drug-induced coma after cardiac

arrest; irreversible neurologic injury; a decision to withhold or withdraw life-sustaining therapies; an expected difficulty in obtaining vascular access for ECMO in the femoral or jugular vein; or a situation in which the ECMO device was not immediately available.

TRIAL PROCEDURES

Randomization was stratified according to center and the duration of ventilation before randomization (<72 hours vs. ≥72 hours). Concealment of the randomized assignment was ensured by means of a centralized, secure, Web-based randomization system. Non-ECMO centers that had extensive expertise in treating patients with ARDS could enter patients if an ECMO retrieval team could establish ECMO within 2 hours after randomization and transfer the patient to the ECMO center. A prespecified protocol was used to treat patients in the control group who had undergone randomization at ECMO centers and at non-ECMO centers (see the Supplementary Appendix).

Patients assigned to the ECMO group underwent percutaneous venovenous cannulation. Anticoagulation was achieved with unfractionated heparin that was adjusted to a target activated partial-thromboplastin time of 40 to 55 seconds or anti-Xa activity between 0.2 and 0.3 IU per milliliter.

Patients in the control group received ventilatory treatment according to the increased recruitment strategy from the Express trial.[5] Neuromuscular blocking agents[15] and prolonged periods of prone positioning[16] were strongly encouraged. Recruitment maneuvers, inhaled nitric oxide, inhaled prostacyclin, or intravenous almitrine could be used when oxygenation objectives were not met. Crossover to ECMO for patients in the control group was allowed if they had refractory hypoxemia (oxygen saturation [Sao_2] of <80% for >6 hours, despite the use of available and feasible adjunctive therapies) and if the treating physician thought that the patient had no irreversible multiorgan failure and that ECMO might change the outcome. For patients who were treated at non-ECMO centers, the mobile ECMO retrieval team was alerted.

END POINTS

The primary end point was mortality at 60 days. The key secondary end point was treatment failure, which was defined as crossover to ECMO or death in patients in the control group and as death in patients in the ECMO group. Other end points included mortality at other time points, the time to death until day 60, and a per-treatment analysis in which mortality was compared among patients who received ECMO and those who did not. Safety end points included the rates of pneumothorax, stroke, infection at the site of ECMO cannula insertion, cannula thrombosis, ECMO circuit change, intravascular hemolysis, ventilator-associated pneumonia, severe hemorrhagic complications, and red-cell transfusion. Other secondary end points are listed in the Supplementary Appendix. Deaths were directly attributed to the ECMO procedure if they occurred in the context of failure of the ECMO device, massive gas emboli, cardiac arrest due to massive circuit clotting, septic shock due to infection at the ECMO cannulation site, intracranial hemorrhage, pneumothorax during cannula insertion, or massive bleeding that led to the transfusion of at least 10 units of packed red cells.

STATISTICAL ANALYSIS

The expected mortality at 60 days was 60% in the group receiving conventional ventilation[5] and was estimated at 40% among those receiving early ECMO support.[13] We calculated that, in order for the trial to have 80% power, at an alpha level of 5% and with a group-sequential analysis occurring after the randomization of every 60 participants, the maximum sample would need to be 331 participants. For the primary end point, a sequential-design method with stopping rules that were defined according to the two-sided triangular test[17] was applied. The two-sided triangular design allowed for early stopping for evidence of superiority of ECMO, a predicted lack of a significant difference, or evidence of harm. More details about the design are given in Section II.2 of the Supplementary Appendix.

The characteristics of the patients at baseline are reported as percentages for categorical variables and as means (with standard deviations) or medians (with interquartile ranges) for continuous variables, as appropriate. Primary analyses were conducted according to the intention-to-treat principle and did not use a stratified test statistic. Categorical variables were compared with chi-square or Fisher's exact tests, and continuous variables were compared with Student's t-test or a Wilcoxon test, as appropriate. Kaplan–Meier survival curves until 60 days after randomization were

compared with a log-rank test. Friedman's tests and other nonparametric tests were used to compare repeated measurements over time. A planned sensitivity analysis was performed with the use of a Cox regression model to adjust for prespecified baseline variables: cause of ARDS, coexisting conditions, age of the patient, duration of mechanical ventilation before randomization, disease severity at inclusion, and center. We conducted post hoc exploratory analyses of the primary end point in subgroups of interest. Given the number of crossover procedures that occurred in patients in the control group, we performed a post hoc rank-preserving structural-failure time analysis to adjust for crossover in the estimation of survival (see the Supplementary Appendix).[18]

All the analyses were conducted at a two-sided alpha level of 5%. All the analyses were performed with the use of R software, version 3.3.3 (R Foundation), except for the sequential analysis of the primary end point, for which we used SAS software, version 9.2 (SAS Institute), and PEST (model-independent parameter estimation and uncertainty analysis) software, version 4 (http://pesthomepage.org).

RESULTS

PATIENTS

After the inclusion of 240 patients, the fourth planned sequential interim analysis (in April 2017) showed that the lower boundary of the stopping-rule triangle had been crossed (Fig. S1 in the Supplementary Appendix). Because no significant between-group difference in mortality at 60 days had been found, trial recruitment was stopped, in accordance with the prespecified rules. Among 1015 patients who were eligible for inclusion, 249 patients underwent randomization: 124 were assigned to the ECMO group and 125 to the control group (Fig. 1). A total of 3 patients in the ECMO group did not receive ECMO (1 patient had rapid clinical improvement and 2 died soon after randomization), and 35 patients (28%) in the control group crossed over to ECMO because of refractory hypoxemia at a mean (±SD) of 6.5±9.7 days after randomization.

The characteristics of the patients at baseline (randomization) were similar in the two groups (Table 1, and Table S1 in the Supplementary Appendix). The main causes of ARDS were bacterial pneumonia (in 45% of the patients) and viral pneumonia (in 18%), and 78% of the patients had severe sepsis or septic shock. Before randomization, 59% of the patients had undergone prone positioning, and 74% had received vasopressors.

TRIAL TREATMENT

Of the 121 patients in the ECMO group who received ECMO at a mean of 3.3±2.8 hours after randomization, insertion of the cannula was performed in the femoral and jugular veins in 116 (96%). A total of 48 of 124 patients (39%) were retrieved from non-ECMO centers by the mobile ECMO rescue team (Table S2 in the Supplementary Appendix). ECMO support lasted a mean of 15±13 days (Fig. S2 in the Supplementary Appendix).

Patients in the ECMO group had tidal volumes, plateau pressures, driving pressures (the difference between the plateau pressure and PEEP), and respiratory rates that decreased from baseline to a greater extent than the respective values in the control group, whereas levels of arterial blood gases in the ECMO group normalized in the immediate days after randomization (Figs. S3 through S6 in the Supplementary Appendix). Patients in the control group, regardless of whether they were treated at ECMO centers or non-ECMO centers, received low-volume, low-pressure ventilation according to the current standard of care (Table S3 and Fig. S7 in the Supplementary Appendix). In the control group, 113 patients (90%) were placed prone, 104 (83%) received inhaled nitric oxide or inhaled prostacyclin, and 100% received neuromuscular blocking agents after randomization (Table 2, and Table S3 in the Supplementary Appendix).

PRIMARY END POINT

At 60 days, 44 patients (35%) in the ECMO group and 57 (46%) in the control group had died (relative risk, 0.76; 95% confidence interval [CI], 0.55 to 1.04; P=0.09) (Table 2). The hazard ratio for death within 60 days after randomization in the ECMO group, as compared with the control group, was 0.70 (95% CI, 0.47 to 1.04; P=0.07) (Fig. 2). Adjustment for important prognostic factors did not change the results.

SECONDARY END POINTS

The relative risk of treatment failure, defined as death by day 60 in patients in the ECMO group and as crossover to ECMO or death in patients

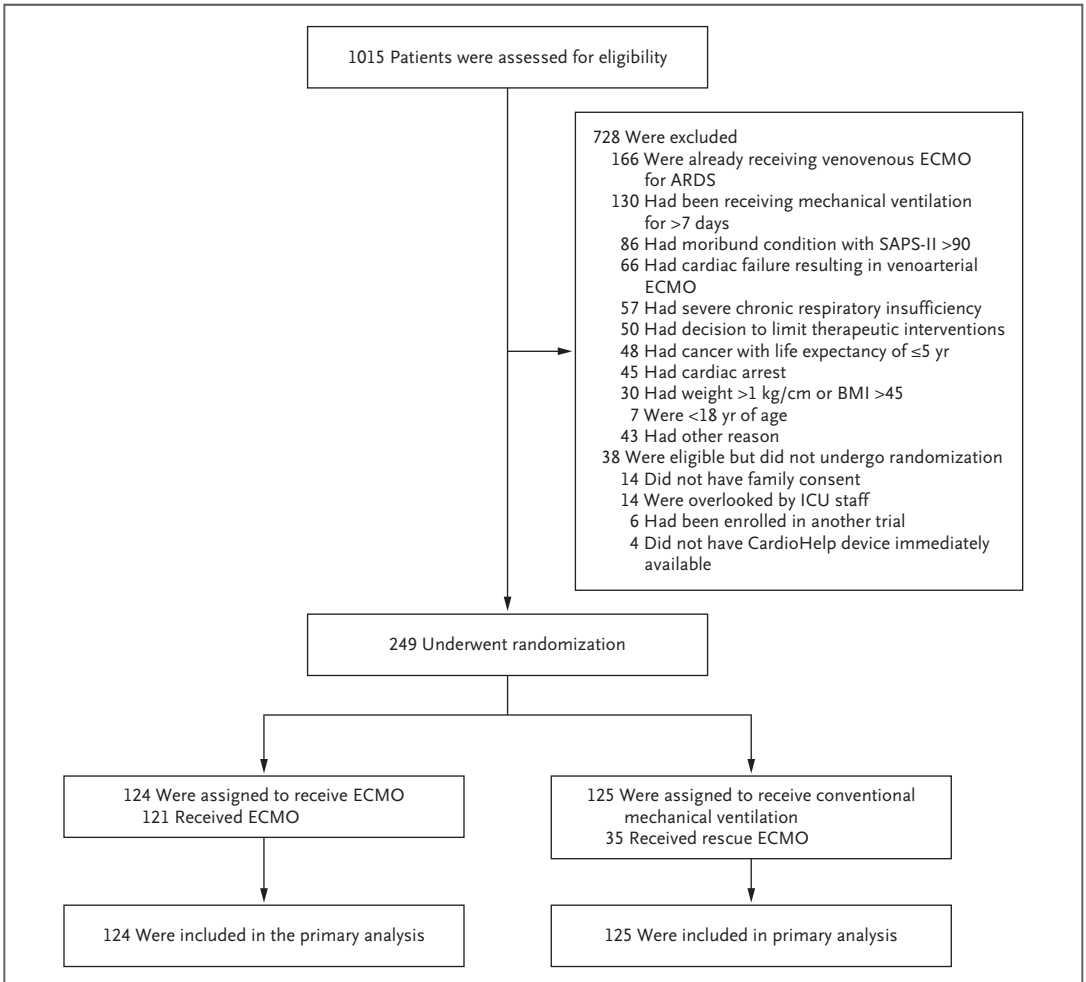

Figure 1. Enrollment, Randomization, and Follow-up of the Trial Participants.

The Simplified Acute Physiology Score (SAPS-II) is assessed on a scale ranging from 0 to 163, with higher scores indicating greater severity of illness. The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters. ARDS denotes the acute respiratory distress syndrome, ECMO extracorporeal membrane oxygenation, and ICU intensive care unit.

in the control group, was 0.62 (95% CI, 0.47 to 0.82; P<0.001) (Table 2, and Table S5 and Fig. S8 in the Supplementary Appendix). At 60 days, patients in the ECMO group had significantly more days than those in the control group without prone positioning (59 vs. 46 days; median difference, 13 days; 95% CI, 5 to 59) and without renal-replacement therapy (50 vs. 32 days; median difference, 18 days; 95% CI, 0 to 51) (Table 2, and Table S6 in the Supplementary Appendix). At 60 days, patients in the ECMO group also had significantly more days than those in the control group that were free from renal failure (46 vs. 21 days; median difference, 25 days; 95% CI, 6 to 53) and cardiac failure (48 vs. 41 days; median difference, 7 days; 95% CI, 0 to 51), according to score-specific organ subcomponents of the Sequential Organ Failure Assessment (Table S6 in the Supplementary Appendix). Multiorgan failure, respiratory failure, and septic shock were the main causes of death in the two groups. Subgroup analyses showed no significant interaction of 60-day mortality with baseline demographic characteristics, ARDS severity, or randomization at ECMO centers versus non-ECMO centers (Fig. S9 in the Supplementary Appendix).

Table 1. Characteristics of the Patients at Randomization.*

Characteristic	ECMO Group (N=124)	Control Group (N=125)
Age — yr	51.9±14.2	54.4±12.7
Male sex — no. (%)	87 (70)	90 (72)
Immunocompromised condition — no. (%)	27 (22)	27 (22)
SOFA score†	10.8±3.9	10.6±3.5
Median time since intubation (interquartile range) — hr	34 (15–89)	34 (17–100)
Cause of ARDS — no. (%)		
Pneumonia		
Bacterial	54 (44)	58 (46)
Viral	26 (21)	20 (16)
Other	44 (35)	47 (38)
Pao_2:FIO_2 — mm Hg	73±30	72±24
PEEP — cm of water	11.7±3.9	11.8±3.7
Tidal volume — ml/kg of predicted body weight	6.0±1.3	6.1±0.9
Respiratory rate — breaths/min	30.4±4.7	31.2±4.5
Plateau pressure — cm of water	29.8±5.5	29.5±4.8
Driving pressure — cm of water	17.8±7.0	17.7±5.8
Respiratory-system compliance — ml/cm of water	25.0±11.5	25.4±10.8
Arterial blood pH	7.24±0.13	7.24±0.12
Pao_2 — mm Hg‡	69±25	68±22
$Paco_2$ — mm Hg	57±15	57±16
Prone positioning — no. (%)§	70 (56)	78 (62)
Inhaled nitric oxide or prostacyclin — no. (%)§	64 (52)	68 (54)
Recruitment maneuvers — no. (%)§	22 (18)	34 (27)
Neuromuscular blockade — no. (%)§	114 (92)	120 (96)

* Plus–minus values are means ±SD. No significant differences were observed between the two groups among the characteristics evaluated at admission to the intensive care unit and at randomization. Data were missing for less than 2% of the patients at randomization, except for data on the plateau pressure and derived variables (driving pressure, which is the difference between the plateau pressure and the positive end-expiratory pressure [PEEP], and respiratory-system compliance), which were missing for 28 patients in the group that received extracorporeal membrane oxygenation (ECMO) and in 30 in the control group. ARDS denotes the acute respiratory distress syndrome, FIO_2 the fraction of inspired oxygen, $Paco_2$ partial pressure of arterial carbon dioxide, and Pao_2:FIO_2 the ratio of the partial pressure of arterial oxygen to the FIO_2.

† Organ failure was assessed with the Sequential Organ Failure Assessment (SOFA) on a scale from 0 to 24, with higher scores indicating more severe organ failure.

‡ The mean FIO_2 was 0.96±0.10 in the ECMO group and 0.96±0.09 in the control group.

§ The use of these interventions was assessed between intubation and randomization.

CROSSOVER TO ECMO

A total of 35 patients (28%) in the control group received ECMO for refractory hypoxemia at a mean of 6.5±9.7 days after randomization (median, 4 days; interquartile range, 1 to 7; range, 0 to 50). These patients had significantly higher values than other patients in the control group with regard to the mean baseline plateau pressure (31.7±5.5 vs. 28.5±4.1 cm of water; mean difference, 3.2 cm of water; 95% CI, 1.2 to 5.2), and driving pressure (20.2±6.1 vs. 16.6±5.3 cm of water; mean difference, 3.6 cm of water; 95% CI, 1.2 to 6.0), had lower respiratory-system compliance (21.3±9.2 vs. 27.1±11.0 ml per centimeter of water; mean difference, −5.8 ml per centimeter of water; 95% CI, −10.4 to −1.1), and had more quadrants with infiltrate in the chest radiograph (3.7±0.6 vs. 3.3±0.9 quadrants; mean difference,

Table 2. End Points.*

End Point	ECMO Group (N=124)	Control Group (N=125)	Relative Risk or Difference (95% CI)†	P Value
Primary end point: mortality at 60 days — no. (%)	44 (35)	57 (46)	0.76 (0.55 to 1.04)	0.09
Key secondary end point: treatment failure at 60 days — no. (%)‡	44 (35)	72 (58)	0.62 (0.47 to 0.82)	<0.001
Other end points				
Mortality at 90 days — no. (%)	46 (37)	59 (47)	−10 (−22 to 2)	
Median length of stay (interquartile range) — days				
In the ICU	23 (13–34)	18 (8–33)	5 (−1 to 10)	
In the hospital	36 (19–48)	18 (5–43)	18 (6 to 25)	
Median days free from mechanical ventilation (interquartile range)§	23 (0–40)	3 (0–36)	20 (−5 to 32)	
Median days free from vasopressor use (interquartile range)§	49 (0–56)	40 (0–53)	9 (0 to 51)	
Median days free from renal-replacement therapy (interquartile range)§	50 (0–60)	32 (0–57)	18 (0 to 51)	
Prone position — no. (%)¶	82 (66)	113 (90)	−24 (−34 to −14)	
Recruitment maneuvers — no. (%)¶	27 (22)	54 (43)	−21 (−32 to −10)	
Inhaled nitric oxide or prostacyclin — no. (%)¶	75 (60)	104 (83)	−23 (−33 to −12)	
Glucocorticoids — no. (%)¶	80 (65)	82 (66)	−1 (−13 to 11)	

* No missing data were observed for patients' outcomes, except for the total duration of hospital stay, for which data were missing for 13 patients in the ECMO group and 14 in the control group. ICU denotes intensive care unit.

† The relative risk for the primary end point with the 95% confidence interval and the P value were corrected for the triangular test. The width of confidence intervals for median differences and absolute risk differences was not adjusted for multiple comparisons and should not be used to infer definitive treatment differences. Difference values for the other end points are presented in percentage points for differences between rates or in days, as appropriate.

‡ The key secondary end point of treatment failure at 60 days was defined as death in patients in the ECMO group and as crossover to ECMO or death in patients in the control group.

§ The number of days free from a particular intervention were calculated with the use of the assignment of 0 days free from the intervention in patients who died during the follow-up period.

¶ Data included the period from randomization to day 60.

0.5 quadrants; 95% CI, 0.1 to 0.8) — all findings that indicate more severe ARDS in the patients who received rescue ECMO (Table S7 in the Supplementary Appendix). At the time that they received ECMO, the median Pao_2:FIO_2 in these patients was 51 mm Hg (interquartile range, 46 to 61), and the median Sao_2 was 77% (interquartile range, 74 to 87). During the 24 hours preceding crossover to ECMO, the Pao_2:FIO_2, Sao_2, and pH values in these patients decreased significantly, and the $Paco_2$ increased significantly (Table S8 in the Supplementary Appendix).

These patients also had signs of rapidly evolving cardiovascular failure, as indicated by the significant increase in the 24 hours before crossover in the median serum lactate level, from 1.7 mmol per liter (interquartile range, 1.3 to 2.2) to 3.2 mmol per liter (interquartile range, 1.5 to 6.2), and in the inotropic score, from 10 μg per kilogram of body weight per minute (interquartile range, 0 to 55) to 90 μg per kilogram per minute (interquartile range, 45 to 215) (Table S8 in the Supplementary Appendix). Before crossover, 9 patients had cardiac arrest, 7 had severe right heart failure, and 11 had renal failure leading to dialysis. Veno-arterial ECMO was applied in 7 patients, including 6 who received ECMO while undergoing cardiopulmonary resuscitation. Mortality at 60 days was 57% (20 of 35 patients) among patients in the control group who crossed over to ECMO versus 41% (37 of 90 patients) among the other patients in the control group (relative risk 1.39; 95% CI, 0.95 to 2.03). The results of the rank-preserving structural-failure time analysis with adjustment for selective crossover are provided in the Supplementary Appendix.

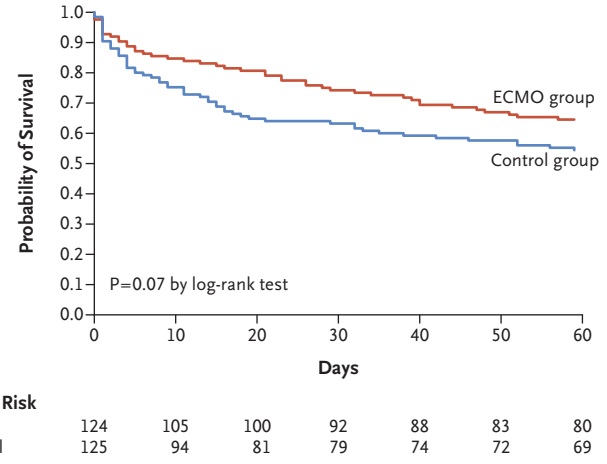

Figure 2. Kaplan–Meier Survival Estimates in the Intention-to-Treat Population during the First 60 Days of the Trial.

ADVERSE EVENTS

One patient in each group died from complications related to ECMO cannulation. Patients in the ECMO group had significantly higher rates than those in the control group of severe thrombocytopenia (<20,000 platelets per cubic millimeter; 27% vs. 16%; absolute risk difference, 11 percentage points; 95% CI, 0 to 21) and bleeding events leading to packed red-cell transfusion (46% vs. 28%; absolute risk difference, 18 percentage points; 95% CI, 6 to 30). The rate of ischemic stroke was lower in the ECMO group than in the control group (no patients vs. 5%; absolute risk difference, –5 percentage points; 95% CI, –10 to –2), but the rate of hemorrhagic stroke was similar in the two groups (Table 3, and Table S9 in the Supplementary Appendix). Rates of pneumothorax, ventilator-associated pneumonia, and massive bleeding were similar in the two groups. Among all the patients who were treated with ECMO, the rate of bleeding was 53%, the rate of hematoma at the cannula-insertion site was 6%, the rate of infection at the cannula-insertion site was 14%, and the rate of intravascular hemolysis was 5%.

DISCUSSION

In this randomized trial involving patients with very severe ARDS, early application of ECMO was not associated with mortality at 60 days (primary end point) that was significantly lower than that in the control group. Although the use of ECMO for severe respiratory failure has increased substantially over the past decade,[19] its use remains controversial.[20] The results of the first two randomized trials of ECMO were disappointing,[21,22] but the trials were conducted decades ago. The results of the most recent trial (Conventional Ventilatory Support versus Extracorporeal Membrane Oxygenation for Severe Adult Respiratory Failure [CESAR]) were encouraging,[13] but not all patients in the ECMO group received ECMO, and the use of mechanical ventilation in the control group lacked standardization. In the present trial, 98% of the patients in the ECMO group received ECMO and were transported during receipt of ECMO to the referral center if needed. Moreover, 90% of the patients in the control group underwent prolonged prone positioning[16] and all of them received neuromuscular blocking agents.[15]

Despite the use of these strategies, which have been shown to improve outcomes,[15,16] 28% of the patients in the control group in our trial crossed over to ECMO for refractory hypoxemia. This crossover rate makes it difficult to draw definitive conclusions regarding the usefulness of ECMO for severe forms of ARDS. We were aware of this potential problem when we started the trial, but many investigators felt that it would have been unethical to prohibit crossover to ECMO in patients with very severe hypoxemia. The prespecified secondary composite end point of death (in both groups) plus crossover to ECMO (in the control group) showed a benefit in favor of the ECMO group, but this is difficult to interpret in light of the negative results for the primary end point. This secondary analysis clearly represents a bias against the control group, but it is important to point out that the patients who crossed over to ECMO were extremely ill (Sao_2 of <80% for >6 hours, despite recruitment maneuvers, inhaled nitric oxide or prostacyclin, and prone positioning; some patients received ECMO during cardiopulmonary resuscitation or received venoarterial ECMO support because of severe cardiac failure). In a sensitivity analysis, results regarding this secondary end point remained significant even under the assumption that one third of these extremely sick patients would have survived without ECMO (Table S5 in the Supplementary Appendix).

Our trial has several limitations. First, it was stopped per protocol after 75% of the maximum calculated sample size had been achieved. Second,

Table 3. Adverse Events as Defined by the Trial Protocol in the Intention-to-Treat Population.

Event	ECMO Group (N=124)	Control Group (N=125)	Absolute Risk Difference (95% CI)*
	number (percent)		*percentage points*
Pneumothorax	18 (15)	16 (13)	2 (–7 to 10)
Thrombocytopenia†			
Any	50 (40)	40 (32)	8 (–4 to 20)
Severe	33 (27)	20 (16)	11 (0 to 21)
Hypothermia‡	28 (23)	27 (22)	1 (–9 to 11)
Bleeding			
Leading to transfusion	57 (46)	35 (28)	18 (6 to 30)
Massive§	3 (2)	1 (1)	2 (–2 to 6)
Cardiac rhythm disturbances	38 (31)	46 (37)	–6 (–18 to 6)
Cardiac arrest	24 (19)	22 (18)	2 (–8 to 12)
Stroke¶	3 (2)	8 (6)	–4 (–10 to 1)
Ischemic stroke	0	6 (5)	–5 (–10 to –2)
Hemorrhagic stroke	3 (2)	5 (4)	–2 (–7 to 3)
Massive stroke	2 (2)	1 (1)	1 (–3 to 5)
Ventilator-associated pneumonia treated with antibiotic agents	48 (39)	46 (37)	2 (–10 to 14)
Gas emboli	0	0	0 (–3 to 3)

* The width of confidence intervals was not adjusted for multiple comparisons and should not be used to infer definitive treatment differences.
† Thrombocytopenia was defined as a platelet count of less than 50,000 per cubic millimeter, and severe thrombocytopenia as a platelet count of less than 20,000 per cubic millimeter.
‡ Hypothermia was defined as a temperature of less than 35°C.
§ A massive bleeding event was defined as hemorrhage leading to the transfusion of more than 10 units of packed red cells.
¶ Hemorrhagic stroke was transformation of ischemic stroke in three of the five patients in the control group. Massive stroke was defined as a score of less than 8 on the Glasgow Coma Scale (on which scores range from 3 to 15, with lower scores indicating a reduced level of consciousness).

the 28% rate of crossover among patients with refractory hypoxemia in the control group may have diluted the potential effect of ECMO. Third, we included patients at ECMO centers and non-ECMO referral centers. However, treatments were strictly defined according to the protocol in each group, and patients who underwent randomization at non-ECMO centers were rapidly transported to a local ECMO center while they were receiving ECMO. Furthermore, ventilatory strategies that were applied in the ECMO centers and non-ECMO centers did not differ among patients in the control group. The inclusion of patients at ECMO centers and non-ECMO referral centers may also be viewed as a strength, since most patients in countries where ECMO is available will be treated initially at non-ECMO centers. Fourth, the trial was probably underpowered to detect mortality that was 20 percentage points lower in the ECMO group than in the control group (in which crossover to ECMO for refractory hypoxemia was allowed).

In conclusion, the analysis of the primary end point (mortality at 60 days) in our trial involving patients with very severe ARDS showed no significant benefit of early ECMO, as compared with a strategy of conventional mechanical ventilation, which included crossover to ECMO (used by 28% of the patients in the control group).

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

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