available at NEJM.org), which estimated that if the trial crossed a futility stopping boundary, the chance of a positive result at full enrollment would be slim. When the trial was stopped, the 60-day mortality was 35% in the ECMO group and 46% in the standard-care group, and the relative risk for death was 0.76 (95% confidence interval [CI], 0.55 to 1.04; P=0.09).

DSMBs typically interpret stopping boundaries as guidelines to be applied with some flexibility. Their decisions are difficult ones, and by their very nature are subject to post hoc evaluation. In this case, the figure shows that the trial had reached but just touched the futility boundary. We are disappointed that the DSMB acted so quickly to stop the trial, but others may have reached the same decision as the DSMB. However, the decision to stop cannot be undone, and this is not the place to debate the wisdom of the decision. It is important to remember that we can learn something positive from a negative trial.[3]

The authors provide two secondary analyses. In the first, the primary outcome in the control group was redefined as death at 60 days or a switch from the standard treatment to ECMO. This end point was reached by 58% of the patients in the control group, as compared with 35% (for death) in the ECMO group, and the relative risk of death or switching was 0.62 (95% CI, 0.47 to 0.82). This end point is difficult to interpret, since switching treatments was at the investigator's discretion and there were no preset specific criteria for a switch from the ECMO group to the control group. The second analysis used a rank-preserving structural-failure time model approach to attempt to recover the causal effect of ECMO. That approach yielded an estimated hazard ratio for death within 60 days of 0.51 (95% CI, 0.24 to 1.02). These three analyses all point to the same conclusion — ECMO probably has some benefit in this context, despite the trial not being traditionally positive. In addition, most of the other secondary outcomes favored ECMO.

The important lessons here are twofold. DSMBs should consider the wider context of a trial — the full landscape of outcomes and alternative analyses that may adjust for aspects of a trial that do not follow the design — and not just the primary outcome when making a stopping decision. Once a trial has been completed, a traditionally negative trial may well be informative with a transparent account of the traditional description of the outcome of a trial along with a thoughtful post hoc analysis.

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

From the Harvard School of Public Health and the Department of Biostatistics and Computational Biology, Dana–Farber Cancer Institute, Boston (D.H.).

1. DeMets DL, Ellenberg SS. Data monitoring committees — expect the unexpected. N Engl J Med 2016;375:1365-71.
2. Combes A, Hajage D, Capellier G, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. N Engl J Med 2018;378:1965-75.
3. Pocock SJ, Stone GW. The primary outcome fails — what next? N Engl J Med 2016;375:861-70.

DOI: 10.1056/NEJMe1805123

ECMO for Severe ARDS

C. Corey Hardin, M.D., Ph.D., and Kathryn Hibbert, M.D.

The acute respiratory distress syndrome (ARDS), which is characterized by severe hypoxemic respiratory failure, affects as many as 10% of patients in the intensive care unit and is a common reason for the use of therapeutic mechanical ventilation.[1] On the basis of results of landmark clinical trials, there is substantial consensus around an initial approach to ARDS that combines invasive mechanical ventilation with limited tidal volumes,[2] the use of positive end-expiratory pressure (PEEP) to prevent derecruitment (the collapse of small airways and alveoli),[3] and conservative fluid management.[4] In patients with severe ARDS, defined as a ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen (Pao_2:Fio_2) of less than 150 mm Hg, heavy sedation with neuromuscular blockade[5] and ventilation in the prone position[6] have been associated with lower mortality. Even so, severe ARDS is associated with mortality that can exceed 40%.[1] Part of the treatment challenge is that mechanical ventilation, which may be lifesaving, may also perpetuate lung

injury because of overdistention of ventilated lung units and repetitive opening and closing of other lung units.[1] One approach that is used to avoid the potentially injurious aspects of mechanical ventilation is extracorporeal membrane oxygenation (ECMO), in which gas exchange occurs by means of an extracorporeal membrane perfused with venous blood.[6]

Although ECMO has been used for decades to support patients with respiratory failure, advances in its technical delivery have been associated with an increase in the number of centers and cases using this approach, particularly since the 2009 H1N1 influenza pandemic.[7] This has occurred despite limited data from high-quality, randomized trials showing convincing evidence of benefit. Until now, the best available evidence to support the use of ECMO was the Conventional Ventilatory Support versus Extracorporeal Membrane Oxygenation for Severe Adult Respiratory Failure (CESAR) trial.[8] Although this trial aimed to compare ECMO with standard of care in patients with severe ARDS, it was weakened by heterogeneous ventilation strategies in the control group (including the use of larger-than-recommended tidal volumes in the control group) and a large percentage of patients in the ECMO group who were transferred to expert centers but never received ECMO. Thus, most practitioners have agreed that there is a need for a large, randomized trial to test the efficacy of ECMO for the treatment of severe ARDS.

In this issue of the *Journal*, Combes et al.[9] present the highly anticipated results of the ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) trial of venovenous ECMO in patients with severe ARDS. The trial design specifically addresses weaknesses of previous trials. Patients who were enrolled in this trial were very sick (Pao_2:Fio_2, <80 mm Hg; respiratory-system compliance, <30 ml per centimeter of water; driving pressure, >16 cm of water; and Sequential Organ Failure Assessment score [on a scale from 0 to 24, with higher scores indicating more severe organ failure], >10 at randomization) and were enrolled within 7 days after the diagnosis of severe ARDS. In addition, unlike in the CESAR trial, patients in the EOLIA trial who had been randomly assigned to ECMO almost universally received it (121 of 124 patients). Lastly, the ECMO approach was highly standardized, and the protocol for ventilator management in the control group reflected the current standard of care. This included ventilation with low tidal volumes, recruitment maneuvers with PEEP, prone positioning (used in 90% of the patients in the control group), and neuromuscular blockade (used in 100%). A large percentage of patients also received inhaled nitric oxide or other adjuvant therapies.

Overall, there was no significant difference in mortality, the primary end point, between the ECMO group and the control group. The interpretation of this end point is complicated by a high percentage of patients (28%) in the control group who crossed over to ECMO in the context of refractory respiratory failure and deteriorating hemodynamics. It is worth noting that the patients who crossed over were identifiably sicker at the time of enrollment than other patients in the control group: they had lower respiratory-system compliance, higher driving pressures, and more extensive infiltrates.[9] Ultimately, they had higher mortality (57%) than patients in the control group who did not cross over to ECMO (41%) and than patients in the ECMO group (35%). Given that the patients who crossed over were potentially identifiable at enrollment, an interesting, but unanswered, question is how their outcomes compared with those in patients in the ECMO group who were comparably sick at the time of enrollment. These data are not presented. In addition, the trial was, controversially,[10] halted before full enrollment after it was determined that the futility threshold had been crossed. Although it is tempting to speculate what the effect of continued enrollment may have been, this is ultimately not knowable.

Nevertheless, at least one important conclusion can be drawn — the routine use of ECMO in patients with severe ARDS is not superior to the use of ECMO as a rescue maneuver in patients whose condition has deteriorated further. This conclusion comes with the important caveat that, to achieve similar results, clinicians ought to use all other evidence-based interventions, including paralysis and prone positioning, and can consider additional rescue maneuvers, including the use of inhaled pulmonary vasodilators. Given the complexity of such a trial and the slow enrollment that occurred in this cohort (249 patients over a period of 6 years), it is unlikely that another trial will be performed in the near future. For now,

clinicians may feel secure with an approach to severe ARDS that combines the above evidence-based interventions while reserving ECMO for patients whose life-threatening hypoxemia persists despite these efforts.

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

From the Department of Pulmonary and Critical Care Medicine, Massachusetts General Hospital, Boston.

1. Thompson BT, Chambers RC, Liu KD. Acute respiratory distress syndrome. N Engl J Med 2017;377:562-72.
2. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000;342:1301-8.
3. Gattinoni L, Caironi P, Cressoni M, et al. Lung recruitment in patients with the acute respiratory distress syndrome. N Engl J Med 2006;354:1775-86.
4. The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med 2006;354:2564-75.
5. Papazian L, Forel J-M, Gacouin A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. N Engl J Med 2010;363:1107-16.
6. Guérin C, Reignier J, Richard JC, et al. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med 2013;368:2159-68.
7. Davies A, Jones D, Bailey M, et al. Extracorporeal membrane oxygenation for 2009 influenza A(H1N1) acute respiratory distress syndrome. JAMA 2009;302:1888-95.
8. Peek GJ, Clemens F, Elbourne D, et al. CESAR: conventional ventilatory support vs extracorporeal membrane oxygenation for severe adult respiratory failure. BMC Health Serv Res 2006;6:163.
9. Combes A, Hajage D, Capellier G, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. N Engl J Med 2018;378:1965-75.
10. Harrington D, Drazen JM. Learning from a trial stopped by a data and safety monitoring board. N Engl J Med 2018;378:2031-2.

DOI: 10.1056/NEJMe1802676

Fast Forward — Neoadjuvant Cancer Immunotherapy

Thomas F. Gajewski, M.D., Ph.D.

Immunotherapies that are based on blocking the axis of the programmed death 1 (PD-1) pathway are having a transformational effect in cancer medicine. To date, the Food and Drug Administration has approved PD-1 pathway inhibitors for 10 types of cancer, with continued clinical study under way. The therapeutic efficacy of these drugs relies on endogenous tumor-antigen–specific T cells that are functionally held in check by negative signaling through PD-1. Preclinical models and human correlative biomarker data indicate that efficacy depends on antitumor CD8+ T cells that are recruited into the tumor microenvironment and that are functionally restrained. Treatment with PD-1 blockade results in an accumulation of functional T cells, which translates into tumor regression.[1] As such, a baseline immune gene signature in tumors correlates with efficacy against PD-1.[2] Antigen-specific T cells that are primed in lymph nodes also are subjected to negative regulation by PD-1 and can expand after treatment. PD-L1 that engages PD-1 on T cells can be expressed by tumor cells, by antigen-presenting cells, or both and is itself induced by the cytokine interferon-γ that is released by T cells undergoing activation,[3] a mechanism that is designed to prevent overactivation of T-cell responses. Thus, a dynamic interaction between CD8+ T cells, antigen-presenting cells, and tumor cells is linked to the efficacy of immunotherapy.

The tumor-associated antigens that are recognized by these CD8+ T cells are diverse, but a major subset arises from nonsynonymous mutations in normal genes that generate new peptide sequences presented by class I major histocompatibility complex molecules.[4] In melanoma, a comparison of tumor-biopsy samples obtained before and after PD-1 blockade revealed the loss of specific mutated sequences among patients who had a response to treatment,[5] which suggests that T cells destroyed neoantigen-expressing tumor cells. Thus, the genomic instability that is a major hallmark of cancer is an Achilles' heel for tumors treated with immune-mediated control.

Most cancer drugs that are active in metastatic disease ultimately are investigated during the postsurgical adjuvant period, when micrometastatic disease and a lower tumor burden may be easier to treat. The PD-1 inhibitor nivolumab was recently approved as adjuvant treatment for resected melanoma on the basis of improved relapse-free survival.[6] However, in contrast to chemotherapy that kills tumor cells directly, PD-1 blockade requires an interaction between T cells, tumor

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 24, 2018 VOL. 378 NO. 21

Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome

A. Combes, D. Hajage, G. Capellier, A. Demoule, S. Lavoué, C. Guervilly, D. Da Silva, L. Zafrani, P. Tirot, B. Veber, E. Maury, B. Levy, Y. Cohen, C. Richard, P. Kalfon, L. Bouadma, H. Mehdaoui, G. Beduneau, G. Lebreton, L. Brochard, N.D. Ferguson, E. Fan, A.S. Slutsky, D. Brodie, and A. Mercat, for the EOLIA Trial Group, REVA, and ECMONet*

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.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Combes at Service de Médecine Intensive–Réanimation, Hôpital Pitié–Salpêtrière, Assistance Publique–Hôpitaux de Paris, Sorbonne Université INSERM, UMRS 1166-ICAN, Institute of Cardiometabolism and Nutrition 47, Boulevard de l'Hôpital, F-75013 Paris, France, or at alain.combes@aphp.fr.

*A list of the investigators in the ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) Trial Group, the Réseau Européen en Ventilation Artificielle (REVA), and the International ECMO Network (ECMONet) is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Brodie and Mercat contributed equally to this article.

N Engl J Med 2018;378:1965-75.
DOI: 10.1056/NEJMoa1800385

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

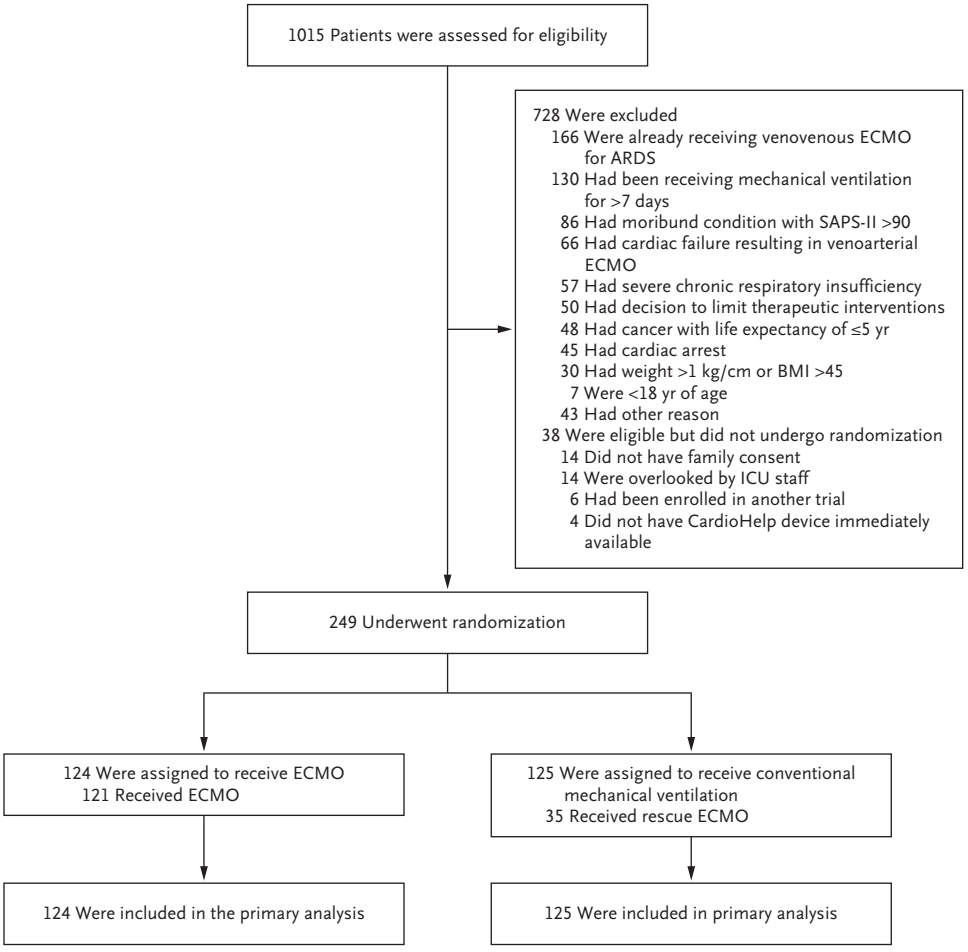

Figure 1. Enrollment, Randomization, and Follow-up of the Trial Participants.

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.

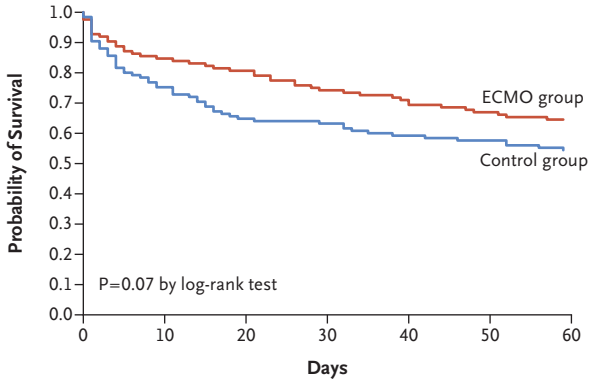

Figure 2. Kaplan–Meier Survival Estimates in the Intention-to-Treat Population during the First 60 Days of the Trial.

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).

Supported by the Direction de la Recherche Clinique et du Développement (DRCD), Assistance Publique–Hôpitaux de Paris (APHP), with a grant from the French Ministry of Health (Programme Hospitalier de Recherche Clinique number, PHRC 2009 081224). International centers that enrolled patients outside France obtained local grants to carry out the trial. An academic

collaboration agreement contract was signed between APHP-DRCD and each international center.

Dr. Combes reports receiving grant support and lecture fees from Maquet and Baxter and consulting fees from Hemovent; Dr. Demoule, receiving lecture fees and loaned equipment for research from Medtronic, grant support and loaned equipment for research from Philips, fees for serving on an advisory board from ResMed, lecture fees and fees for serving on an advisory board from Baxter, lecture fees from Hamilton Medical, and lecture fees and payment of registration fee from Fisher and Paykel; Dr. Levy, receiving grant support from Getinge France; Dr. Brochard, receiving grant support from Medtronic–Covidien, grant support and loaned equipment for research from Air Liquide and Fisher and Paykel, and loaned equipment for research from General Electric and Philips; Dr. Slutsky, receiving consulting fees from Novalung–Xenios, Baxter, and Maquet Critical Care; Dr. Brodie, receiving fees for serving on an advisory board and fees for serving on a steering committee, paid to his institution, from ALung Technologies, and fees for serving on an advisory board, paid to his institution, from Kadence Healthcare (Johnson & Johnson); and Dr. Mercat, receiving fees for serving on a steering committee from Faron Pharmaceuticals, consulting fees from Air Liquide Medical Systems, grant support and lecture fees from Fisher and Paykel and Covidien, and lecture fees from Pfizer, ResMed, and Dräger. No other potential conflict of interest relevant to this article was reported.

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

APPENDIX

The authors' full names and academic degrees are as follows: Alain Combes, M.D., Ph.D., David Hajage, M.D., Ph.D., Gilles Capellier, M.D., Ph.D., Alexandre Demoule, M.D., Ph.D., Sylvain Lavoué, M.D., Christophe Guervilly, M.D., Daniel Da Silva, M.D., Lara Zafrani, M.D., Ph.D., Patrice Tirot, M.D., Benoit Veber, M.D., Ph.D., Eric Maury, M.D., Ph.D., Bruno Levy, M.D., Ph.D., Yves Cohen, M.D., Ph.D., Christian Richard, M.D., Ph.D., Pierre Kalfon, M.D., Ph.D., Lila Bouadma, M.D., Ph.D., Hossein Mehdaoui, M.D., Gaëtan Beduneau, M.D., Ph.D., Guillaume Lebreton, M.D., Ph.D., Laurent Brochard, M.D., Ph.D., Niall D. Ferguson, M.D., Eddy Fan, M.D., Ph.D., Arthur S. Slutsky, M.D., Daniel Brodie, M.D., and Alain Mercat, M.D., Ph.D.

The authors' affiliations are as follows: Sorbonne Université INSERM Unité Mixte de Recherche (UMRS) 1166, Institute of Cardiometabolism and Nutrition (A.C., G.L.), Service de Médecine Intensive–Réanimation, Institut de Cardiologie, Assistance Publique–Hôpitaux de Paris (APHP) Hôpital Pitié–Salpêtrière (A.C.), Département de Biostatistiques, Santé Publique et Information Médicale, Centre de Pharmacoépidémiologie, APHP Hôpital Pitié–Salpêtrière (D.H.), Sorbonne Université, Unité de Recherche Clinique Pitié–Salpêtrière (D.H.), Sorbonne Université INSERM UMRS 1158 (A.D.), Service de Médecine Intensive–Réanimation et Pneumologie, APHP Hôpital Pitié–Salpêtrière (A.D.), Service de Médecine Intensive et Réanimation, Centre Hospitalier Universitaire (CHU) Saint Louis (L.Z.), Service de Médecine Intensive et Réanimation, CHU Saint Antoine (E.M.), Service de Médecine Intensive et Réanimation, APHP Bichat Hospital, Diderot University (L. Bouadma), and Service de Chirurgie Thoracique et Cardiovasculaire, APHP Hôpital Pitié–Salpêtrière, Institut de Cardiologie (G.L.), Paris, Service de Médecine Intensive et Réanimation, Besançon University Hospital, and Research Unit Equipe Avenir 3920 and Structure Fédérative de Recherche 4234, University of Franche Comté, Besançon (G.C.), Service de Médecine Intensive et Réanimation, CHU Pontchaillou, Rennes (S.L.), Service de Médecine Intensive et Réanimation, CHU Hôpital Nord, APHM, Marseille (C.G.), Service de Médecine Intensive et Réanimation, CHU Saint Denis, Saint Denis (D.D.S.), Service de Médecine Intensive et Réanimation, CHU Le Mans, Le Mans (P.T.), Département d'Anesthésie et Réanimation, CHU de Rouen (B.V.), Service de Médecine Intensive et Réanimation, Rouen University Hospital (G.B.), and Normandie University, Université de Rouen, Equipe Avenir 3830, Rouen University Hospital (G.B.), Rouen, Service de Médecine Intensive et Réanimation, CHU Nancy and INSERM Unité 1116, Université de Lorraine, Nancy (B.L.), Service de Médecine Intensive et Réanimation, CHU Avicenne, Bobigny (Y.C.), Service de Médecine Intensive et Réanimation, CHU Kremlin Bicêtre, Le Kremlin Bicêtre (C.R.), Service de Réanimation Polyvalente, Hôpital de Chartres, Chartres (P.K.), CHU Martinique, Fort-de-France (H.M.), and Service de Médecine Intensive et Réanimation, Centre Hospitalier Universitaire d'Angers, Université d'Angers, Angers (A.M.) — all in France; the Interdepartmental Division of Critical Care Medicine, Departments of Medicine and Physiology, Institute for Health Management, Policy, and Evaluation, University of Toronto (L. Brochard, N.D.F., E.F.), Keenan Research Center, Li Ka Shing Knowledge Institute, St. Michael's Hospital (L. Brochard, A.S.S.), and the Department of Medicine, Division of Respirology, University Health Network and Sinai Health System, Toronto General Hospital (N.D.F., E.F.), Toronto; and the Division of Pulmonary, Allergy, and Critical Care Medicine, Columbia University Medical Center, and New York–Presbyterian Hospital, Columbia University, New York (D.B.).

REFERENCES

1. Thompson BT, Chambers RC, Liu KD. Acute respiratory distress syndrome. N Engl J Med 2017;377:562-72.
2. Slutsky AS, Ranieri VM. Ventilator-induced lung injury. N Engl J Med 2013;369:2126-36.
3. Bellani G, Laffey JG, Pham T, et al. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. JAMA 2016;315:788-800.
4. Sud S, Friedrich JO, Taccone P, et al. Prone ventilation reduces mortality in patients with acute respiratory failure and severe hypoxemia: systematic review and meta-analysis. Intensive Care Med 2010;36:585-99.
5. Mercat A, Richard JC, Vielle B, et al. Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. JAMA 2008;299:646-55.
6. Brodie D, Bacchetta M. Extracorporeal membrane oxygenation for ARDS in adults. N Engl J Med 2011;365:1905-14.
7. Combes A, Brodie D, Bartlett R, et al. Position paper for the organization of extracorporeal membrane oxygenation programs for acute respiratory failure in adult patients. Am J Respir Crit Care Med 2014;190:488-96.
8. Combes A, Pesenti A, Ranieri VM. Fifty years of research in ARDS: is extracorporeal circulation the future of acute respiratory distress syndrome management? Am J Respir Crit Care Med 2017;195:1161-70.
9. Schmidt M, Zogheib E, Rozé H, et al. The PRESERVE mortality risk score and analysis of long-term outcomes after extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. Intensive Care Med 2013;39:1704-13.
10. Davies A, Jones D, Bailey M, et al. Extracorporeal membrane oxygenation for 2009 influenza A(H1N1) acute respiratory distress syndrome. JAMA 2009;302:1888-95.
11. Noah MA, Peek GJ, Finney SJ, et al. Referral to an extracorporeal membrane oxygenation center and mortality among patients with severe 2009 influenza A(H1N1). JAMA 2011;306:1659-68.

12. Pham T, Combes A, Rozé H, et al. Extracorporeal membrane oxygenation for pandemic influenza A(H1N1)-induced acute respiratory distress syndrome: a cohort study and propensity-matched analysis. Am J Respir Crit Care Med 2013;187:276-85.
13. Peek GJ, Mugford M, Tiruvoipati R, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. Lancet 2009;374:1351-63.
14. Bernard GR, Artigas A, Brigham KL, et al. The American-European Consensus Conference on ARDS: definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 1994;149:818-24.
15. Papazian L, Forel JM, Gacouin A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. N Engl J Med 2010;363:1107-16.
16. Guérin C, Reignier J, Richard JC, et al. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med 2013;368:2159-68.
17. Sébille V, Bellissant E. Comparison of the two-sided single triangular test to the double triangular test. Control Clin Trials 2001;22:503-14.
18. Ishak KJ, Proskorovsky I, Korytowsky B, Sandin R, Faivre S, Valle J. Methods for adjusting for bias due to crossover in oncology trials. Pharmacoeconomics 2014;32:533-46.
19. Karagiannidis C, Brodie D, Strassmann S, et al. Extracorporeal membrane oxygenation: evolving epidemiology and mortality. Intensive Care Med 2016;42:889-96.
20. Hubmayr RD, Farmer JC. Should we "rescue" patients with 2009 influenza A(H1N1) and lung injury from conventional mechanical ventilation? Chest 2010;137:745-7.
21. Zapol WM, Snider MT, Hill JD, et al. Extracorporeal membrane oxygenation in severe acute respiratory failure: a randomized prospective study. JAMA 1979;242:2193-6.
22. Morris AH, Wallace CJ, Menlove RL, et al. Randomized clinical trial of pressure-controlled inverse ratio ventilation and extracorporeal CO2 removal for adult respiratory distress syndrome. Am J Respir Crit Care Med 1994;149:295-305.

EDITORIALS

Learning from a Trial Stopped by a Data and Safety Monitoring Board

David Harrington, Ph.D., and Jeffrey M. Drazen, M.D.

One of the reasons we conduct clinical trials to test specific aspects of patient care is to be sure that the interventions we do benefit patients. As clinicians, we are well aware that the outcomes of a treatment may vary substantially from one participant to another; a treatment that works spectacularly well in one person is ineffective in another. If a trial is too small, an average treatment effect favoring an intervention may be consistent with the play of chance. Trials with larger numbers of participants measure average treatment effects more precisely and are more likely to detect real intervention effects. However, larger trials put more participants at risk for side effects or for being treated with an ineffective regimen. Trial design and monitoring is a delicate balancing act between putting the fewest people at risk and learning the most about a given therapy.

The problem of protecting participants in a trial is not new. A widely used solution has been to form data and safety monitoring committees (or boards), often known as DSMBs. Members of a DSMB bring to the table expertise in the clinical area under study, in trial design, and in statistics[1] but do not have the potential conflicts of interests that trial investigators may have. A DSMB reviews trial data while the trial is enrolling, sometimes unmasked with respect to trial-group assignment, and can provide advice to stop the trial if the treatment under study shows clear efficacy or has side effects that outweigh its potential benefit. The DSMB can also stop a trial for futility if a reasonable projection can be made on the basis of current outcomes and enrollment that the trial will be unlikely to reject a null hypothesis of no treatment effect.

This last aspect of the remit of DSMBs can be one of the most difficult to carry out. Stopping a trial early for futility may have lasting implications on what we know about a treatment. Early stopping for futility precludes the certainty we seek in clinical trials — the outcome will often be neither definitively positive nor negative such that estimates of the effects of a treatment will not have the benefit of the larger sample size that was originally planned. If the protocol allowed patients to be switched from the control group for lack of efficacy, the estimated treatment effect can be diluted toward the null hypothesis of no difference. These negative effects of early stopping for futility must, of course, be balanced against the ethics of continued randomization in a trial that seems headed for a negative outcome.

In the trial conducted by Combes et al.,[2] the results of which are reported in this issue of the *Journal*, we have an important example of a dilemma faced by a DSMB. This trial compared 60-day mortality among patients with severe acute respiratory distress syndrome (ARDS) who had been assigned to standard ventilator care or to treatment with extracorporeal membrane oxygenation (ECMO). The very nature of the intervention meant that the clinicians caring for the patients in this trial were aware of the trial-group assignments. Therefore, a patient in the standard-care group could be switched, if the responsible clinician so wished, to ECMO if a patient continued to have severe hypoxemia despite maximal non-ECMO treatment. After the enrollment of 240 of a projected maximum of 331 patients, the trial was stopped for futility, per the trial design (Fig. S1 in the Supplementary Appendix of the article,

available at NEJM.org), which estimated that if the trial crossed a futility stopping boundary, the chance of a positive result at full enrollment would be slim. When the trial was stopped, the 60-day mortality was 35% in the ECMO group and 46% in the standard-care group, and the relative risk for death was 0.76 (95% confidence interval [CI], 0.55 to 1.04; P=0.09).

DSMBs typically interpret stopping boundaries as guidelines to be applied with some flexibility. Their decisions are difficult ones, and by their very nature are subject to post hoc evaluation. In this case, the figure shows that the trial had reached but just touched the futility boundary. We are disappointed that the DSMB acted so quickly to stop the trial, but others may have reached the same decision as the DSMB. However, the decision to stop cannot be undone, and this is not the place to debate the wisdom of the decision. It is important to remember that we can learn something positive from a negative trial.[3]

The authors provide two secondary analyses. In the first, the primary outcome in the control group was redefined as death at 60 days or a switch from the standard treatment to ECMO. This end point was reached by 58% of the patients in the control group, as compared with 35% (for death) in the ECMO group, and the relative risk of death or switching was 0.62 (95% CI, 0.47 to 0.82). This end point is difficult to interpret, since switching treatments was at the investigator's discretion and there were no preset specific criteria for a switch from the ECMO group to the control group. The second analysis used a rank-preserving structural-failure time model approach to attempt to recover the causal effect of ECMO. That approach yielded an estimated hazard ratio for death within 60 days of 0.51 (95% CI, 0.24 to 1.02). These three analyses all point to the same conclusion — ECMO probably has some benefit in this context, despite the trial not being traditionally positive. In addition, most of the other secondary outcomes favored ECMO.

The important lessons here are twofold. DSMBs should consider the wider context of a trial — the full landscape of outcomes and alternative analyses that may adjust for aspects of a trial that do not follow the design — and not just the primary outcome when making a stopping decision. Once a trial has been completed, a traditionally negative trial may well be informative with a transparent account of the traditional description of the outcome of a trial along with a thoughtful post hoc analysis.

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

From the Harvard School of Public Health and the Department of Biostatistics and Computational Biology, Dana–Farber Cancer Institute, Boston (D.H.).

1. DeMets DL, Ellenberg SS. Data monitoring committees — expect the unexpected. N Engl J Med 2016;375:1365-71.
2. Combes A, Hajage D, Capellier G, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. N Engl J Med 2018;378:1965-75.
3. Pocock SJ, Stone GW. The primary outcome fails — what next? N Engl J Med 2016;375:861-70.

DOI: 10.1056/NEJMe1805123

ECMO for Severe ARDS

C. Corey Hardin, M.D., Ph.D., and Kathryn Hibbert, M.D.

The acute respiratory distress syndrome (ARDS), which is characterized by severe hypoxemic respiratory failure, affects as many as 10% of patients in the intensive care unit and is a common reason for the use of therapeutic mechanical ventilation.[1] On the basis of results of landmark clinical trials, there is substantial consensus around an initial approach to ARDS that combines invasive mechanical ventilation with limited tidal volumes,[2] the use of positive end-expiratory pressure (PEEP) to prevent derecruitment (the collapse of small airways and alveoli),[3] and conservative fluid management.[4] In patients with severe ARDS, defined as a ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen (Pao_2:Fio_2) of less than 150 mm Hg, heavy sedation with neuromuscular blockade[5] and ventilation in the prone position[6] have been associated with lower mortality. Even so, severe ARDS is associated with mortality that can exceed 40%.[1] Part of the treatment challenge is that mechanical ventilation, which may be lifesaving, may also perpetuate lung