EDITORIAL

# Time for Clinicians to Embrace Their Inner Bayesian?
## Reanalysis of Results of a Clinical Trial of Extracorporeal Membrane Oxygenation

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**This issue of *JAMA*** includes a Special Communication by Goligher et al[1] reporting a Bayesian reanalysis of the results from the recent Extracorporeal Membrane Oxygenation (ECMO) to Rescue Lung Injury in Severe Acute Respiratory Distress Syndrome (ARDS) (EOLIA) trial. This trial, which tested whether routine early ECMO reduced mortality for patients with severe ARDS, was stopped early for futility, and concluded that ECMO was not shown to reduce mortality.[2] In contrast, Goligher et al found it highly probable that ECMO lowers mortality, incorporating various assumptions, although it is unclear whether the benefit is as large as that assumed when the EOLIA trial was designed. How can the conclusions drawn from these 2 analyses of the same trial be so different?

Related article

### Frequentist vs Bayesian Inference

Frequentist statistics focus on the probability with which differences in outcomes between 2 groups (one treated with the experimental therapy and the other not), or differences more extreme, would occur by chance alone.[3] In common practice, if the chance (*P* value) is less than .05, the conclusion is that chance alone cannot account for the differences seen and thus the treatment affects outcome. This approach is algorithmic and familiar. Proponents argue the approach also has rigor because it does not rely on subjective assumptions. Its drawbacks include (1) the inability to express the probability of benefit quantitatively when framing a trial as simply positive or negative; (2) the approach is counterintuitive and prone to frequent misinterpretation; (3) findings of no difference between groups may occur because the assumed treatment effect was unreasonably high (a choice that is subjective); and (4) there is limited ability to interpret results in the context of what else is known about the intervention.

In contrast, Bayesian inference directly estimates the probability that a conclusion is true given the data observed in an experiment, without any requirement that the conclusion is binary. Bayes' theorem mathematically combines prior information (prior data and beliefs) with new data (eg, the results of a new trial) to yield an updated summary of knowledge and the remaining uncertainty.[4] Specifically, a prior probability function, summarizing the prior information, is combined with a likelihood function, summarizing all information contained in the new data, to create a posterior probability function that represents the updated information. Bayesian analyses produce probability statements regarding the truth of a conclusion, such as in the analysis of Goligher and colleagues[1] there was a 92% probability that the absolute risk reduction (ARR) in mortality associated with ECMO was greater than 2%. Proponents argue that such statements are more likely than *P* values to be interpreted correctly by clinicians and patients and that Bayesian inference is more intuitive, aligning conceptually with the way humans typically judge whether something might be true.

Bayes' theorem also provides a framework for sequential learning: the current posterior probability function naturally serves as the prior function for the interpretation of future data. Its major drawbacks include (1) relative lack of familiarity within the medical research community; and (2) concerns that the reliance on subjective prior information will render the conclusions suspect or invalid.

### The Case for or Against ECMO for Severe ARDS

Severe ARDS can lead to hypoxic death despite mechanical ventilation and intensive care. When first introduced, ECMO was shown to provide effective gas exchange but with frequent complications.[5] ECMO has become safer, but other treatment options for ARDS have also improved. Against this changing clinical landscape, multiple trials and observational studies comparing ECMO with other treatments have yielded conflicting results. Expert opinions are highly variable on the role of ECMO, and EOLIA was intended to settle the debate. The trial was powered to test whether use of ECMO for very severe ARDS would reduce mortality from an anticipated 60% to 40% (ARR of 20%; relative risk [RR] of 0.67) when compared with a supportive care group that permitted late use of ECMO if necessary. The data and safety monitoring board stopped the trial early for futility. With 249 patients randomized, the observed mortality rate was 11% lower in the ECMO group (35% in the ECMO group vs 46% in the control group) but not statistically significant (*P* = .09). Furthermore, 28% of patients in the control group received ECMO. Rather than settling the debate, the study fueled it anew, with multiple conflicting opinions expressed regarding the interpretation of the trial.[6-11]

### Bayesian Interpretation of the EOLIA Trial

By using a Bayesian approach, Goligher et al calculated the entire distribution of probabilities regarding the potential benefit of ECMO (eg, the probability that ECMO provides any benefit [RR <1], at least a 2% ARR, at least 4% ARR, and so on up to that tested in the trial: ≥20% ARR and RR <0.67). Their analysis




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incorporated the data from the EOLIA trial, which are fixed and known, and prior information, which must be defined and can be varied. They approached the definition of prior information in 2 ways: mathematical representations of differing opinions (skeptical, neutral, and enthusiastic) and from a meta-analysis of prior studies, further discounting previous results by various amounts to reflect differing estimates of their relevance.

The goal of repeating the analysis with differing prior information is to determine the sensitivity of the results to differing prior beliefs that might be held by diverse clinicians or other stakeholders. If the qualitative interpretation of the trial is dependent on a particular prior, then individuals with different prior beliefs would reasonably interpret the trial results differently. Alternatively, if the results change minimally, the conclusion is that the findings should be interpreted consistently. Broadly speaking, the probability estimates regarding whether ECMO had any effect (RR <1) were independent of choice of prior (ranging from 88%-99% probability that ECMO reduces mortality).[1] Meanwhile, the probability that ECMO reduced mortality by at least 20% was low and variable (range, 0%-48%).[1] Thus, the Bayesian analyses support a consensus that ECMO lowers mortality but, at the same time, demonstrate that there remains substantial variability in the conclusions to be drawn regarding whether ECMO confers a large benefit. In contrast, the original frequentist analysis was silent with regard to whether ECMO had any effect and only supported the conclusion that the results from the EOLIA trial cannot support a finding of large benefit.[2]

## Caveats to the Bayesian Approach

A Bayesian analysis is only transparent to the degree that individuals understand the information represented in the prior distributions—both the magnitude of the assumed treatment effect and the strength of that assumption. Thus, although Goligher et al calculated the probability of benefit across a range of priors, an important issue is whether the range represents the full diversity of informed prior opinion. For example, a prior distribution may indicate a belief that ECMO is protective but allow for tremendous uncertainty and thus convey very little information. There are no standard prior distributions for summarizing clinical opinions, and terms like *strongly enthusiastic* or *moderately pessimistic* may be applied to markedly different probability distributions. Therefore, communicating the strength and content of a prior is often best done graphically or by stating the number of equivalent patient outcomes and the associated treatment effect that the prior distribution represents (see Table 1 of Goligher et al).

In the article by Goligher et al, the use of prior information derived from a meta-analysis of prior trials illustrates the type of sequential updating of knowledge that is a strength of the Bayesian approach.[4] However, given ubiquitous differences in the details of trials (eg, differences in patient populations, settings, interventions, and outcome measures), prior and current trials may not be estimating the same treatment effect. To account for differences in opinion regarding the similarity of prior ECMO trials with the EOLIA trial, Goligher et al downweighted the prior information from the meta-analysis by decreasing the effective number of patients by 0%, 25%, 50%, and 75%. This downweighting maintained the same mean treatment effect but widened the uncertainty around it. By providing a range of downweighting, Goligher et al permitted readers to see all information and select that which corresponds to their personal belief regarding the degree with which prior trials and the current trial are similar.

## What Next?

Even though Goligher et al focused on ECMO, there are many therapies in medicine for which there is conflicting evidence and varying opinion. Using ECMO as an example, it is clear that a Bayesian framework provides a wider, and arguably more informative, set of interpretations than that typically provided by a frequentist analysis. The Bayesian approach also provides an explicit quantitative display of factors that are often weighed internally and subjectively by experts when forming treatment recommendations.

Although the Bayesian approach appears explicit, much must be specified to understand its assumptions. Thus, if Bayesian analyses are to be used more commonly, 2 specific conditions are important. First, investigators should outline their proposed approach explicitly, in detail, and ideally before launching any new clinical trial. In that way, their analysis plan could undergo peer review, their selection of prior information may be vetted, and the design of the trial may be improved. Second, for consistency, rigor, and reproducibility, it is important to develop a set of standards for both the conduct and reporting of Bayesian analyses, similar to those widely adopted for other assessment methodologies, like clinical trials, meta-analyses, and cost-effectiveness analyses.[12-14]

The debate should not be cast as frequentist vs Bayesian inference: there is no need to choose. Rather, a better goal may be simply to promote greater and more rigorous use of Bayesian analyses as either a primary or a complementary tool for clinicians, patients, and policymakers. In addition, the findings of Goligher et al may help those evaluating ECMO to think differently about what questions are next. Clinicians and researchers should no longer ask "Does ECMO work?" because that question appears to be answered. Instead, the key question that should now be asked is "By how much does ECMO work, in whom, and at what cost?"


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**Published Online:** October 22, 2018. doi:10.1001/jama.2018.16916

**Conflict of Interest Disclosures:** All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Lewis is the Senior Medical Scientist at Berry Consultants, a statistical consulting firm that specializes in the design, implementation, analysis and oversight of Bayesian adaptive clinical trials. Dr Angus reports consulting for Beckman Coulter, Bristol-Myers Squibb, Bayer AG, and GenMARK and being the chair of the clinical trial steering committee for Ferring Pharmaceuticals.

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JAMA | Special Communication | CARING FOR THE CRITICALLY ILL PATIENT

# Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome and Posterior Probability of Mortality Benefit in a Post Hoc Bayesian Analysis of a Randomized Clinical Trial

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**IMPORTANCE** Bayesian analysis of clinical trial data may provide useful information to aid in study interpretation, especially when trial evidence suggests that the benefits of an intervention are uncertain, such as in a trial that evaluated early extracorporeal membrane oxygenation (ECMO) for severe acute respiratory distress syndrome (ARDS).

**OBJECTIVE** To demonstrate the potential utility of Bayesian analyses by estimating the posterior probability, under various assumptions, that early ECMO was associated with reduced mortality in patients with very severe ARDS in a randomized clinical trial (RCT).

**DESIGN AND EVIDENCE** A post hoc Bayesian analysis of data from an RCT (ECMO to Rescue Lung Injury in Severe ARDS [EOLIA]) that included 249 patients with very severe ARDS who had been randomized to receive early ECMO (n = 124; mortality at 60 days, 35%) vs initial conventional lung-protective ventilation with the option for rescue ECMO (n = 125, mortality at 60 days, 46%). The trial was designed to detect an absolute risk reduction (ARR) of 20%, relative risk (RR) of 0.67. Statistical prior distributions were specified to represent varying levels of preexisting enthusiasm or skepticism for ECMO and by Bayesian meta-analysis of previously published studies (with downweighting to account for differences and quality between studies). The RR, credible interval (CrI), ARR, and probability of clinically important mortality benefit (varying from RR less than 1 to RR less than 0.67 and ARR from 2% or more to 20% or more) were estimated with Bayesian modeling.

**FINDINGS** Combining a minimally informative prior distribution with the findings of the EOLIA trial, the posterior probability of RR less than 1 for mortality at 60 days after randomization was 96% (RR, 0.78 [95% CrI, 0.56-1.04]); the posterior probability of RR less than 0.67 was 18%, the probability of ARR of 2% or more was 92%, and the probability of ARR of 20% or more was 2%. With a moderately enthusiastic prior, equivalent to information from a trial of 264 patients with an RR of 0.78, the estimated RR was 0.78 (95% CrI, 0.63-0.96), the probability of RR less than 1 was 99%, the probability of RR less than 0.67 was 8%, the probability of ARR of 2% or more was 97%, and the probability of ARR of 20% or more was 0%. With a strongly skeptical prior, equivalent to information from a trial of 264 patients with an RR of 1.0, the estimated RR was 0.88 (95% CrI, 0.71-1.09), the probability of RR less than 1 was 88%, the probability of RR less than 0.67 was 0%, the probability of ARR of 2% or more was 78%, and the probability of ARR of 20% or more was 0%. If the prior was informed by previous studies, the estimated RR was 0.71 (95% CrI, 0.55-0.94), the probability of RR less than 1 was 99%, the probability of RR less than 0.67 was 48%, the probability of ARR of 2% or more was 98%, and the probability of ARR of 20% or more was 4%.

**CONCLUSIONS AND RELEVANCE** Post hoc Bayesian analysis of data from a randomized clinical trial of early extracorporeal membrane oxygenation compared with conventional lung-protective ventilation with the option for rescue extracorporeal membrane oxygenation among patients with very severe acute respiratory distress syndrome provides information about the posterior probability of mortality benefit under a broad set of assumptions that may help inform interpretation of the study findings.

*JAMA*. doi:10.1001/jama.2018.14276
Published online October 22, 2018.

Editorial
Supplemental content

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The conventional frequentist approach to statistical analysis of clinical trials evaluates study hypotheses indirectly by estimating the probability that a treatment effect the same or larger than the observed treatment effect would be obtained if the null hypothesis (which generally assumes that there is no treatment effect) was true. The goal of frequentist analysis is to determine whether the evidence leads one to confidently reject the null hypothesis. In Bayesian analysis, information available prior to the trial about the plausible range of values of the treatment effect (represented as a probability distribution) is updated by the data collected in the trial to produce a revised estimate of the plausible range of values of the treatment effect.[1] Bayesian analysis informs clinical decisions by directly estimating the probability of a hypothesized treatment effect given the observed data.[2,3] In addition, because information about treatment effect from preexisting clinical and biological evidence is formally incorporated into statistical evaluation, Bayesian methods explicitly quantify the otherwise implicit influence of clinical judgment and prior beliefs on the interpretation of trial results.[4-6]

A recent randomized clinical trial (RCT) of extracorporeal membrane oxygenation (ECMO), ECMO to Rescue Lung Injury in Severe ARDS (EOLIA),[7] offers an example of the potential value of Bayesian analysis. In this trial, the effect of early ECMO on mortality in very severe acute respiratory distress syndrome (ARDS) did not reach statistical significance ($P$ = .09 in the primary analysis). However, the clinically important point estimate of the absolute risk difference (11%), the near statistical significance of the effect despite early stopping for futility, and the wide divergence of preexisting views regarding the benefit of ECMO[8,9] (due in part to differences between prior studies and their potential methodological limitations) have made interpretation of the trial controversial.[10-12] In this Special Communication, a post hoc Bayesian analysis of this trial demonstrating the potential utility of the Bayesian approach is presented.

## Key Points

**Question** Can Bayesian analysis clarify the interpretation of clinical trial results?

**Findings** In a post hoc Bayesian analysis of the recent EOLIA (Extracorporeal Membrane Oxygenation [ECMO] to Rescue Lung Injury in Severe ARDS) trial, the posterior probability of mortality benefit (relative risk <1) ranged between 88% and 99% given a range of prior assumptions reflecting varying degrees of skepticism and enthusiasm regarding previous evidence for the benefit of ECMO. Probabilities varied according to the definition of minimum clinically important mortality benefit; for example, the posterior probability of relative risk less than 0.67 ranged between 0% and 48% given the same range of prior assumptions.

**Meaning** Information about the posterior probability of treatment effect provided by Bayesian analysis may help clarify the interpretation of clinical trial findings.

## Methods

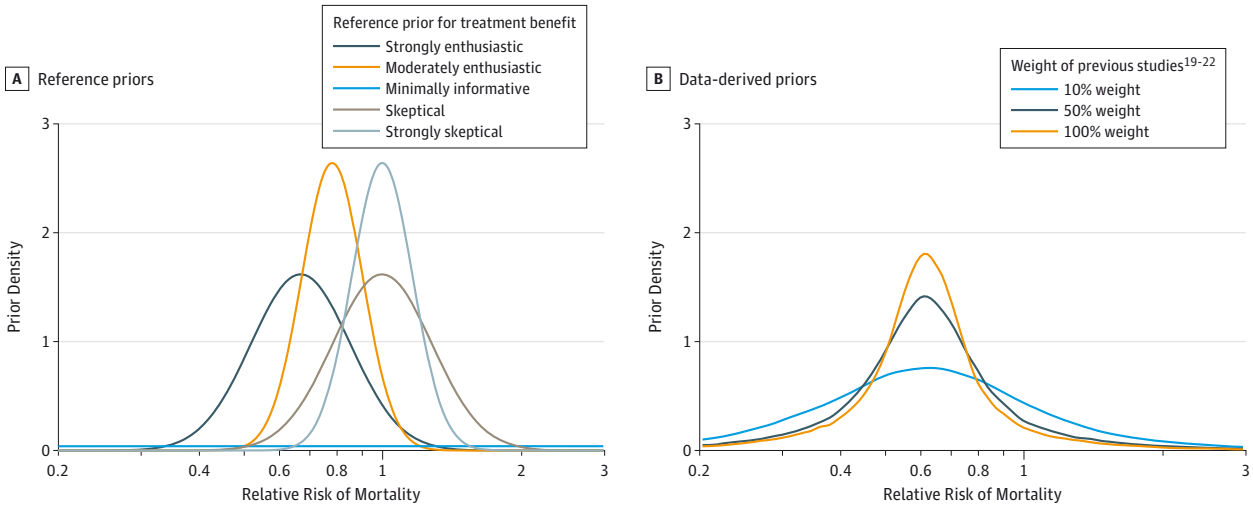
The EOLIA trial received ethical approval from the ethics committees at all participating sites. The EOLIA trial was a multicenter, international RCT designed to test the hypothesis that early venovenous ECMO reduces 60-day mortality in patients with very severe forms of ARDS ($Pao_2/Fio_2$ <50 mm Hg for >3 hours; $Pao_2/Fi\,o_2$ <80 mm Hg for >6 hours; or pH <7.25 and $Paco_2$ ≥60 mm Hg with a maximum plateau pressure of 32 cm $H_2O$ and respiratory rate set at 35 breaths per minute for ≥6 hours).[7] The trial was designed to detect a decrease in mortality risk from 60% to 40% (absolute risk reduction [ARR] of 20%, relative risk [RR] of 0.67).

This article presents a previously unplanned reanalysis of the prespecified primary end point conducted using Bayesian methods. The aim was to estimate the posterior probabilities that the treatment effect exceeded a range of potential values for the minimum clinically important treatment effect (RR <1, RR <0.9, RR <0.8, RR <0.67; and ARR ≥2%, ARR ≥4%, ARR ≥6%, ARR ≥8%, ARR ≥10%, and ARR ≥20%, assuming a baseline mortality risk of 46% based on the EOLIA control group). This range of possible values for the minimum clinically important treatment effect incorporated several considerations. First, because the null hypothesis under frequentist conventions in the trial was "no benefit" (RR = 1), the probability of any mortality benefit (RR<1) was estimated. Second, ARR values of 2% were deemed to be a reasonable potential minimum clinically important effect because this would be equivalent to an estimated 500 lives saved every year in the United States (assuming approximately 25 000 cases of very severe ARDS annually in the United States based on a population of 328 million persons,[13] an annual incidence of ARDS of 80 per 100 000 population,[14] and a prevalence of very severe ARDS of approximately 10% among all cases of ARDS[15]). However, arguments can be made supporting a lower RR or larger ARR as a minimal clinically important difference, and the trial was designed to detect an RR less than 0.67 and an ARR of 20% or more; therefore, the posterior probabilities across a range of effect sizes were computed.

Bayesian analysis represents prior beliefs about the plausible range of values for treatment effect as a probability density distribution. The width (variance) of this distribution represents the level of certainty about the treatment effect, whereas the area under the distribution to the left of any given value is the probability that the parameter (RR or ARR) is smaller than that value (for examples, see **Figure 1** and Table 1). Two approaches were used to develop statistical priors for this analysis. First, priors were used to reflect varying degrees of enthusiasm and skepticism for the benefit of ECMO before the trial. A minimally informative reference prior (which regards all possible log-relative risk values to be equally likely) was used to produce results essentially dependent on data from the trial alone; this prior adds minimal information to the trial in calculating posterior probabilities.

A range of reference priors were defined to represent strongly enthusiastic, moderately enthusiastic, skeptical, and strongly skeptical archetypes of prior belief about the probability of benefit from early ECMO consistent with preexisting controversy among experts in the field[8,16] (**Table 1**). Each prior distribution was characterized by a different assumed value for median RR (the value for RR that an enthusiast or skeptic would assume to have a 50% probability of obtaining) and a different width (variance, representing the magnitude of uncertainty about the plausible range of values for treatment effect). To aid in understanding the strength of the enthusiasm or skepticism represented by these theoretical priors, the sample size and observed

**Figure 1. Reference and Data-Derived Priors Showing the Plausible Range of Values for Differing RRs of Mortality With the Use of Early ECMO in Patients With Very Severe ARDS**




ARDS indicates acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; RR, relative risk. Bayesian analysis combines each prior distribution with the likelihood function of the observed treatment benefit in the trial to determine the posterior probability of treatment benefit. A, A range of reference prior distributions were specified in an effort to match the spectrum of belief within the clinical community about the benefit of ECMO. The minimally informative prior distribution posits that all potential values for log-relative risk are equally likely. B, The data-derived priors were based on previous studies (see Methods for details). To account for likely differences in previous studies, the weight (influence) of patients enrolled in these previous studies was reduced by artificially inflating the study variance (resulting in a wider prior probability density distribution).

**Table 1. Characteristics of Reference Prior Probability Distributions Representing Prior Beliefs About Mortality Benefit From ECMO in Patients With Very Severe ARDS**

| Prior Belief | Assumed Median RR | Assumed SD of Logarithm of RR | Prior Evidence Equivalent[a] | Probability of Treatment Effect ≥Specified Threshold, % | | | | Rationale for Specifying Distribution Characteristics |
|---|---|---|---|---|---|---|---|---|
| | | | | RR <1 | RR <0.9 | RR <0.8 | RR <0.67 | |
| Minimally informative | 1.0 | 10 | Equivalent to essentially no prior belief | 50 | 50 | 49 | 49 | All possible values for treatment effect for log RR are equally likely |
| Strongly enthusiastic | 0.67 | 0.25 | Equivalent to a previous RCT enrolling 100 patients finding 33% RR reduction | 95 | 89 | 77 | 58 | Probability of observing a treatment effect ≥that assumed in EOLIA trial design is 50%; probability of harm (RR >1) is 5% |
| Moderately enthusiastic | 0.78 | 0.15 | Equivalent to a previous RCT enrolling 264 patients finding 22% RR reduction | 95 | 83 | 57 | 24 | Probability of observing a treatment effect ≥that approximating effect observed in ARDSNet lower tidal volumes trial (RR = 0.78) is 50%; probability of harm (RR >1) is 5% |
| Skeptical | 1.0 | 0.24 | Equivalent to a previous RCT enrolling 100 patients finding 0% RR reduction | 50 | 33 | 18 | 7 | Probability of observing a treatment effect ≥that assumed in EOLIA trial design (RR = 0.67) is 5%; probability of benefit and harm are equivalent |
| Strongly skeptical | 1.0 | 0.15 | Equivalent to a previous RCT enrolling 264 patients finding 0% RR reduction | 50 | 24 | 7 | 1 | Probability of observing a treatment effect ≥that observed in the ARDSNet lower tidal volume trial (RR = 0.78) is 5% |

Abbreviations: ARDS, acute respiratory distress syndrome; ARDSNet, National Institutes of Health/National Heart, Lung, and Blood Institute ARDS Network; ECMO, extracorporeal membrane oxygenation; EOLIA, ECMO to Rescue Lung Injury in Severe ARDS; RCT, randomized clinical trial; RR, relative risk.

[a] Prior evidence equivalent communicates the level of certainty represented in each reference prior by reference to the treatment effect and sample size of a hypothetical RCT required to generate the level of informative influence on posterior probability specified by the reference prior relative to the size of the EOLIA trial.

RR were computed for a hypothetical clinical trial achieving the same level of certainty in the treatment effect as each prior. This sample size was computed by comparing the variance of each prior distribution to the variance of the log-relative risk observed in the trial (Table 1).

In accordance with previously published recommendations,[9,15] the priors were defined so as to represent enthusiastic or skeptical viewpoints with respect to (1) the probability that the true effect of ECMO on mortality is the same or greater than that used to power the trial (ie, RR ≤0.67) or than the effect observed in the ARDSNet trial of low tidal volume ventilation (a classic trial in the treatment of ARDS, RR <0.78)[17] and (2) the probability that ECMO would worsen mortality (ie, RR >1). Reference priors specified on this basis are described in detail in Table 1. Figure 1A depicts the probability density distribution for RR specified by each reference prior distribution.

Table 2. Probability of Treatment Effects Estimated by Bayesian Analysis According to Varying Prior Beliefs About Mortality Benefit From ECMO in Patients With Very Severe ARDS

| Prior Belief | Posterior Median RR (95% Credible Interval) | Posterior Probability That True RR Is <Specified Threshold, % | | | |
|---|---|---|---|---|---|
| | | RR <1 | RR <0.9 | RR <0.8 | RR <0.67 |
| Reference prior distributions | | | | | |
| Minimally informative | 0.78 (0.56-1.04) | 96 | 85 | 60 | 18 |
| Strongly enthusiastic | 0.74 (0.57-0.95) | 99 | 94 | 73 | 22 |
| Moderately enthusiastic | 0.78 (0.63-0.96) | 99 | 91 | 61 | 8 |
| Skeptical | 0.84 (0.64-1.07) | 93 | 73 | 39 | 5 |
| Strongly skeptical | 0.88 (0.71-1.09) | 88 | 58 | 18 | 0 |
| Data-derived prior distributions | | | | | |
| No downweighting of previous studies[a] | 0.71 (0.55-0.94) | 99 | 96 | 83 | 48 |
| 50% downweighting of previous studies | 0.73 (0.56-0.96) | 99 | 94 | 77 | 40 |
| 75% downweighting of previous studies | 0.74 (0.56-0.98) | 98 | 92 | 72 | 36 |

Abbreviation: RR, relative risk.

[a] Downweighting refers to a deliberate reduction in the influence (weight) of previous studies in the Bayesian hierarchical model by artificially increasing the variance of these studies. Downweighting provides a method of representing uncertainty about the estimates of effect in these studies given their likely differences (methodological limitations?) compared with the current trial.

Second, data-derived prior distributions were developed based on relevant studies[18-20] from a meta-analysis of ECMO for ARDS.[21] The treatment effects in these previous studies were combined with the observed data from this trial in a Bayesian hierarchical random-effects model (that itself used minimally informative priors). The previous studies generated a prior for what the treatment effect in the "next" study would be, a prior that is combined with data from this trial to produce an updated distribution of the estimated treatment effect after this trial. To reflect concerns about possible differences between the current and previous studies (eg, nonrandomized design in 2 studies, confounding by transfer to specialist centers, or suboptimal control group management), the variance of the previous studies was inflated so that patients in preexisting studies were "downweighted" to exert less influence (ie, received less weight in the analysis) on the pooled estimate of effect. Downweighting was applied to varying degrees so that patients in previous studies exerted between 0% and 100% of the weight of patients enrolled in the trial. It allowed the uncertainty about the estimates of effect in studies given their likely differences (methodological limitations?) to be mathematically represented. The effects and level of uncertainty described by the data-derived priors are represented graphically in Figure 1B.

Separate Bayesian models were run for each of the prior distributions on the log-relative risk for ECMO. The likelihood function (the probability of observing the data collected in the trial for each possible value of RR) was computed for the trial. Each model treated the numbers of deaths in the ECMO and control groups as independent samples from binomial distributions and placed a uniform prior on the probability of death in the control group ($p_c$) so that the probability in the ECMO group was RR × $p_c$. Markov chain Monte Carlo modeling (with 3 chains, 20 000 iterations burn-in and 20 000 saved iterations per chain) was used to derive treatment effect estimates and 95% credible intervals (CrIs) from the median, 2.5th and 97.5th percentiles of the posterior distribution, and to estimate the posterior probabilities of treatment effects exceeding certain thresholds. The ARR was calculated from the RR for a fixed baseline mortality risk of 46%. The Gelman-Rubin statistic was used to assess convergence of all models. All analyses were conducted in R (R Foundation), version 3.5.0, using R2jags[22] to run JAGS.[23]

## Results

### Bayesian Analysis Using a Minimally Informative Prior

Posterior probabilities of ARRs and RR reductions in mortality for a range of priors are shown in **Table 2** and **Table 3**. **Figure 2** presents both the likelihood function for the trial and the posterior probability distribution for RR reductions for each prior. With the minimally informative prior, the estimated median RR for mortality at 60 days with early ECMO was 0.78 (95% CrI, 0.56-1.04). The posterior probability of mortality benefit with early ECMO (ie, RR <1) was 96%, the probability of RR less than 0.67 was 18%. Assuming a baseline mortality risk of 46%, the probability of ARR of 2% or more was 92%, and the probability of ARR of 20% or more was 2% (Table 3).

### Bayesian Analysis Using Reference Priors

The posterior probability of RR less than 1 exceeded 90% across the strongly enthusiastic, moderately enthusiastic, and skeptical priors (Table 2, Figure 2). In the most extreme case of a strongly skeptical prior the estimated RR was 0.88 (95% CrI, 0.71-1.09), the posterior probability of RR less than 1 was 88%, the probability of RR less than 0.67 was 0%, the probability of ARR of 2% or more was 78%, and the probability of ARR of 20% or more was 0%.

### Bayesian Analysis Using the Data-Derived Priors

When combining treatment effects from previous studies with the data from the trial in the hierarchical model, estimated RR in the trial was 0.71 (95% CrI, 0.55-0.94). With this prior, the posterior probability of RR less than 1 was 99%, probability of RR less than 0.67 was 48%, the probability of ARR of 2% or more was 98%, and the probability of ARR of 20% or more was 4%.

When the previous studies were downweighted to account for their likely methodological limitations by up to 90%, the upper limit of the 95% CrI for treatment effect fell below 1 and the probability of RR less than 1 exceeded 90% (**Figure 3**). The probability

Table 3. Probability That Early ECMO Reduces Mortality by a Proposed Minimum Clinically Important Difference According to Varying Prior Beliefs About Mortality Benefit From ECMO in Patients With Very Severe ARDS

| Prior Belief | Posterior Median ARR, % (95% Credible Interval) | Posterior Probability That True ARR Is ≥Specified Threshold, %[a] | | | | | |
|---|---|---|---|---|---|---|---|
| | | 2% | 4% | 6% | 8% | 10% | 20% |
| Reference prior distributions | | | | | | | |
| Minimally informative | 10.6 (−1.8 to 20.0) | 92 | 86 | 78 | 67 | 53 | 2 |
| Strongly enthusiastic | 12.0 (2.1 to 19.9) | 98 | 95 | 89 | 79 | 65 | 2 |
| Moderately enthusiastic | 10.4 (2.0 to 17.2) | 97 | 93 | 85 | 71 | 51 | 0 |
| Skeptical | 7.8 (−3.4 to 16.5) | 86 | 76 | 62 | 47 | 30 | 0 |
| Strongly skeptical | 5.6 (4.1 to 13.3) | 78 | 63 | 45 | 26 | 13 | 0 |
| Data-derived prior distribution | | | | | | | |
| No downweighting of previous studies | 13.6 (2.9 to 20.5) | 98 | 96 | 93 | 88 | 79 | 4 |
| 50% Downweighting of previous studies | 12.8 (1.9 to 20.4) | 97 | 95 | 91 | 83 | 72 | 3 |
| 75% Downweighting of previous studies | 12.1 (1.1 to 20.3) | 97 | 93 | 88 | 79 | 66 | 3 |

Abbreviations: ARDS, acute respiratory distress syndrome; ARR. absolute risk reduction; ECMO, extracorporeal membrane oxygenation; EOLIA, ECMO to Rescue Lung Injury in Severe ARDS.

[a] ARR was computed assuming a baseline mortality risk of 46% (based on the mortality rate in the EOLIA control group).

of RR less than 0.67 and ARR of 20% or more remained low across the range of downweighting (Table 2 and Figure 3).

## Discussion

Bayesian analysis constitutes an alternative to the conventional approach for the statistical evaluation of medical hypotheses. Rather than estimating the probability of the data given the hypothesis, it aims to estimate the probability of the hypothesis given the data. Statisticians have long identified either as "Bayesians" or as "frequentists"[2]; the debate turns, in part, on the role of deductive vs inductive inference in scientific reasoning.[24] In 2010, the US Food and Drug Administration finalized guidelines for the application of Bayesian statistics in trial design and interpretation in clinical trials of medical devices.[25] Bayesian analysis may suggest differing conclusions from frequentist analysis, particularly when observed effect sizes are relatively large but statistical power is relatively low.[3]

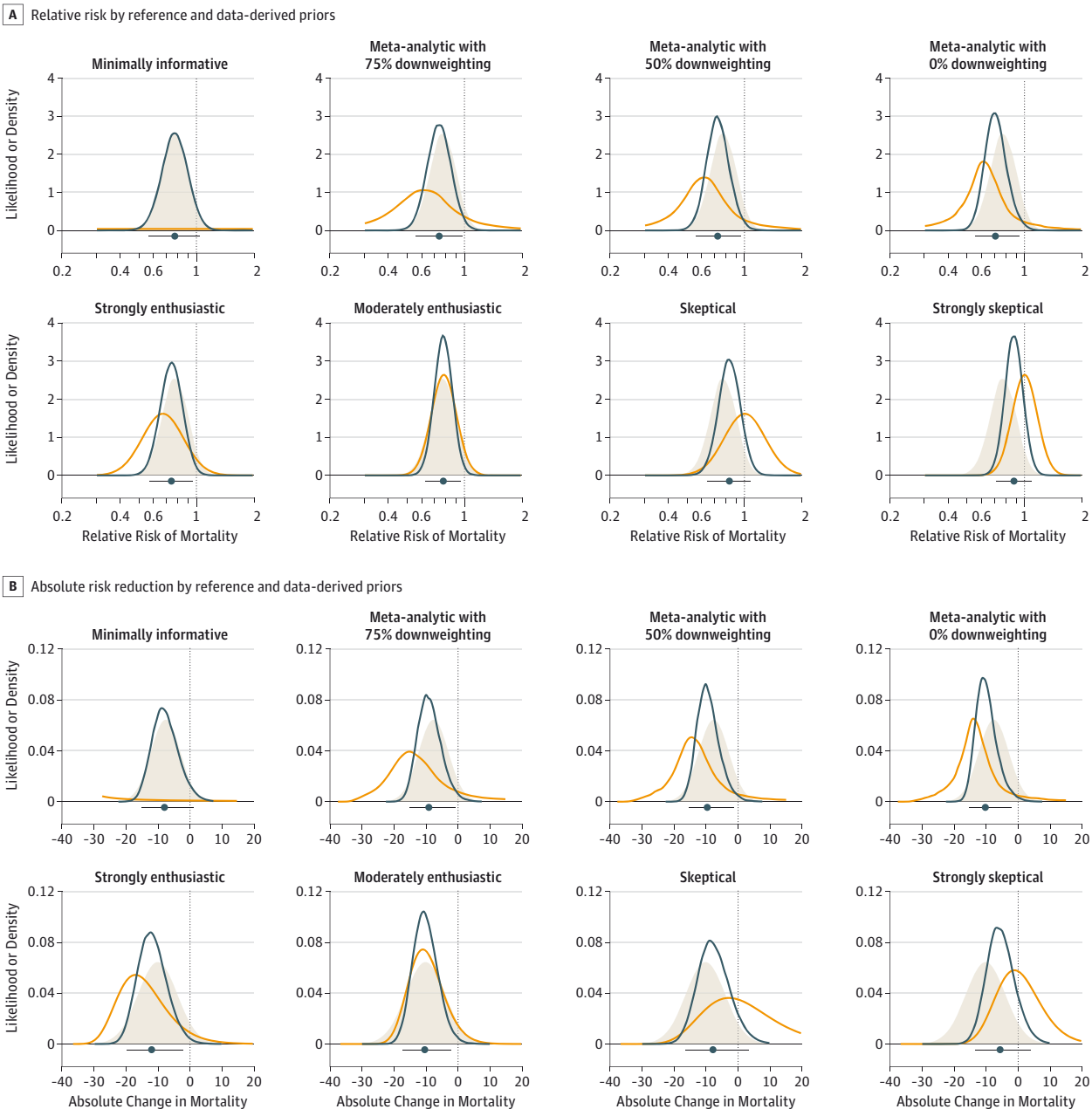
In the original description of the EOLIA trial, the investigators concluded that "early application of ECMO was not associated with mortality at 60 days that was significantly lower than that in the control group."[7] This conclusion appropriately reflects the frequentist approach to hypothesis testing. The probability of observing an absolute mortality difference of 11% or more under the null hypothesis of no treatment effect was not sufficiently low to warrant the rejection of the null hypothesis according to frequentist conventions (RR, 0.76 [95% CI, 0.55-1.04], $P$ = .09, in the primary analysis). This conclusion may be at variance with clinical and scientific intuition as it discounts altogether the clinically relevant effect size and a 95% CI that lies mostly below 1. The difficulty of interpreting the results of this frequentist analysis was immediately evident with one editorial concluding that "the routine use of ECMO in patients with severe ARDS is not superior to the use of ECMO as a rescue maneuver,"[11] whereas another suggested that "ECMO probably has some benefit in this context."[26]

The statement that ECMO probably has some benefit is an intuitive expression of the Bayesian approach to data analysis. The Bayesian framework aims to define the probability of a desired treatment effect rather than to rule out the absence of any treatment effect. Bayesian analysis of the EOLIA trial demonstrates that across a range of prior assumptions about the probability of benefit from early ECMO, the posterior probability of any mortality benefit (RR <1) with early ECMO is high, ranging between 88% to 99%. The influence of priors on the posterior probability varied with the definition of treatment effect, particularly for ARR. For an ARR of 2% or more, the posterior probability of benefit ranged between 78% and 98%, depending on the prior. For an ARR of 20% or more, the posterior probability ranged from 0% to 2%.

The analyses described highlight several advantages of the Bayesian framework. First, the use of statistical priors permits the wide spectrum of opinion within the clinical community regarding any treatment to be formally incorporated in the analysis. This is particularly important with ECMO. In a Bayesian analysis of a previous clinical trial of ECMO in children published in 1989,[19] Kass and Greenhouse observed that "diverse opinions among knowledgeable and thoughtful observers arise because ... different people attach different degrees of importance to various pieces of information concerning the merits of the treatment."[27] By incorporating these varying background beliefs as priors, Bayesian analysis can quantify the overall strength of evidence in support of a hypothesis, complementing conventional frequentist approaches to hypothesis testing in clinical trials.

Second, Bayesian methods directly estimate the probability that the treatment effect is larger than a clinically important threshold, given prior assumptions; such information may be more directly informative to clinicians and patients or families wrestling with complex treatment decisions than probabilities of observing data more extreme than the observed data if there is no real treatment effect quantified by frequentist $P$ values. The probabilistic results of Bayesian analysis naturally align with the thought processes of clinicians making treatment decisions at the bedside

Figure 2. Posterior Probability Distributions for RR and ARR Based on EOLIA Trial Results for the Benefit of Early ECMO on Mortality in Patients Very With Severe ARDS, by Reference and Data-Derived Priors

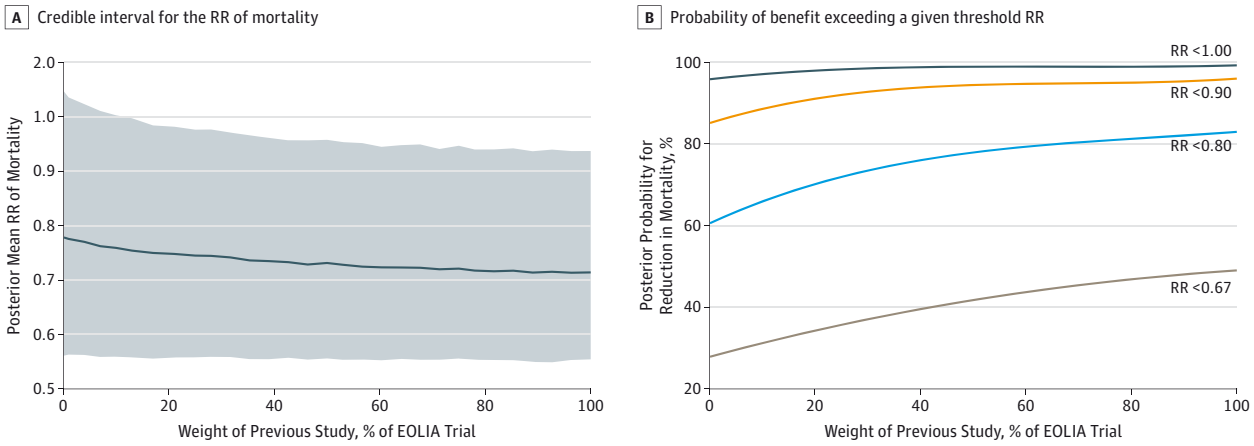



ARR indicates absolute risk reduction; ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; EOLIA, ECMO to Rescue Lung Injury in Severe ARDS; RR, relative risk. Orange lines indicate the reference or data-derived priors. The green-shaded areas indicate the treatment effect observed EOLIA trial (likelihood function). Blue lines indicate posterior probability distribution. The blue point and line below each set of distributions indicates the posterior median effect and 95% credible interval. The vertical dotted line indicates where RR = 1 to provide a visual reference point. Reference or data-derived priors are combined with the likelihood function summarizing the treatment effect observed in the EOLIA trial to compute the posterior probability for the treatment effect. The likelihood function summarizing the trial data is the same across all priors; variation in the posterior distribution arises from variation in the prior. In the minimally informative reference prior, the likelihood function and posterior distribution are identical. This approach allows assessment of the influence of prior enthusiasm or skepticism for early ECMO on the interpretation of the trial.

where the probabilities of various competing benefits and harms must be weighed.

Third, by representing what is known about the treatment effect through a probability distribution, Bayesian analysis allows the probabilities for different magnitudes of treatment effect to be estimated. For the purposes of analysis, we defined an ARR of 2% as a potential threshold for clinically important treatment effect. However, this threshold may be insufficient to motivate the routine use

**Figure 3. Posterior Probabilities for a Reduction in Mortality With Early ECMO Given the EOLIA Trial and the Results of Previous Studies[19-22] in Patients With Very Severe ARDS**




ECMO indicates extracorporeal membrane oxygenation; EOLIA, ECMO to Rescue Lung Injury in Severe ARDS; RR, relative risk. Varying degrees of weight were applied to the previous studies by artificially increasing the variance (width) of their probability distribution to reflect varying levels of confidence in their estimates of effect given their likely differences (and potential methodological limitations). A, This panel shows the resulting credible intervals (blue-shaded area) for the RR of mortality for various levels of weighting of previous studies in proportion to the weight assigned to the EOLIA trial. B, This panel shows the resulting estimated posterior probability that the RR for mortality exceeds each threshold value.

of early ECMO. Indeed, with an ARR threshold of 20%, the posterior probability was 2%. Various factors must be weighed in defining the minimum clinically important effect: the baseline risk of the outcomes, the relevance of the outcome under study, the resources and expertise required to deliver the intervention, the risk of treatment-related adverse effects, and the effect on other clinical outcomes. Given uncertainty over this value, posterior probabilities for a range of ARR and RR reductions were reported. Further investigation using decision analysis may help to define the optimal value for clinically important treatment effect.

Fourth, Bayesian posterior probabilities can also inform the question of whether future trials are required. For example, some might propose conducting yet another RCT of early ECMO to confirm mortality benefit (RR <1) under frequentist conventions (ie, $P < .05$). The posterior probabilities reported here can help to inform future discussions about the need for additional trials and whether the ethical requirement for equipoise in an RCT can be satisfied. Decisions about the need for a future trial depend on the definition of equipoise (probability of benefit sufficient to exclude equipoise) and the definition of the minimum clinically important treatment effect.[28]

There are challenges with Bayesian analysis. First, given their significant influence on posterior probabilities, the priors must be specified to appropriately reflect the evidence available before the trial. Selection of priors therefore requires careful thought. Bayesian analysis also requires decisions about the minimum clinically important treatment effect, as discussed above. Because decisions about priors and treatment effects inevitably incorporate an element of judgement, Bayesian analysis is sometimes criticized for perceived subjectivity. To address these challenges, posterior probabilities were computed for a wide range of potential values of minimum clinically important treatment effect under a range of reference priors specified based on other considerations and on prior data.

Second, the data-derived prior was estimated based on previous studies deemed to be of acceptable methodological quality (RCTs and observational studies employing rigorous propensity score techniques for analysis). Because the methodological limitations of these studies reduced confidence in their estimates of effect,[21,29] the weight of these studies was reduced in the Bayesian hierarchical model to render them less informative in the construction of the prior. Reassuringly, the probability of treatment benefit remained high, even when these studies were downweighted such that a patient in the preexisting studies contributed much less influence in comparison with a patient enrolled in the EOLIA trial.

Third, reference priors were specified based on previous recommendations for establishing representative levels of enthusiasm and skepticism.[1,3] This approach permits assessment of prior probability both in terms of existing clinical data and the strength of the biological plausibility. Readers should determine which prior best matches their own background assessment of the prior probability of benefit from ECMO in very severe ARDS and assess the posterior probability of benefit in light of the EOLIA trial accordingly. One important decision is the specification of the strongly skeptical reference prior; this requires a judgment about the upper limit of reasonable skepticism. The strongly skeptical reference prior specified for this analysis is equivalent to the information derived from a hypothetical trial of early ECMO enrolling 264 patients (6% more than the EOLIA trial) that finds no difference in the risk of death in treatment and control groups. Because there are no studies of this magnitude published in the current ECMO era, this prior distribution appears to appropriately represent the upper limit of reasonable prior skepticism.

Fourth, whether the findings of this Bayesian analysis support the routine use of early ECMO for very severe ARDS remains a matter of judgment. This judgment must incorporate several considerations: the distribution of prior probability, the probability of

mortality benefit (level of certainty) required to motivate action (ie, should one apply a treatment that has a predicted probability of benefit of 70% vs 80% vs 90%), the minimum clinically important treatment effect size, the effect on outcomes other than mortality (ie, long-term functional status, quality of life, costs, resource implications), and the risk of adverse events. This is particularly important because physicians often underestimate the risk of adverse events. This complexity highlights the need for decision analyses; Bayesian posterior probability distributions very naturally inform decision analysis.[1] The decision to initiate ECMO will always remain complex; no clinical trial, however conclusive, can remove the role of clinical judgment in making decisions about treatments. The findings of this Bayesian analysis may be helpful to inform these judgments.

## Limitations

Limitations of this analysis include those inherent in the primary trial. Premature termination and a high rate of crossovers may have led to limited statistical power to detect a meaningful treatment effect. Patients were enrolled from both ECMO centers and non-ECMO referral centers, resulting in delayed ECMO initiation for some patients, although this reflects clinical practice given the regionalized nature of ECMO services.

In addition, there are limitations specific to these Bayesian reanalyses. First, the present analysis constitutes an unplanned post hoc analysis of trial data. Such analyses should generally be treated with caution (ie, regarded as hypothesis-generating only) because, among other concerns, repeated hypothesis testing using different analyses increases the chance of erroneously concluding that the null hypothesis can be rejected (*P* hacking).[30] Several considerations, however, suggest that the present analyses are less vulnerable to these concerns. They tested the same hypothesis and analyzed the same prespecified primary end point as in the original publication—the prespecified hypothesis or primary outcome were not revised (generally entailed in secondary analyses). In addition, under Bayesian analysis, the risk of erroneously estimating the posterior probability of treatment effect arises from incorrectly specifying the priors, not from repeated estimates of this probability. The capacity to allow repeated estimates of posterior probability is the basis for Bayesian adaptive trial design.[31]

Second, because the analyses were planned after the trial was published, it was difficult to use empirical methods to elicit prior beliefs about the benefit of ECMO; beliefs about benefit would unavoidably be influenced by the results of the EOLIA trial.[32] Empirically derived priors might have helped to clarify the extent to which the EOLIA trial should modify the perceived probability of benefit. Recognizing this limitation, a range of priors was specified to represent the range of potential prior beliefs about treatment effect that might have been described by an empirical method.

Third, these analyses focused specifically on mortality and did not consider other adverse events, which given the technological challenges of ECMO would be important to consider.

## Conclusions

Post hoc Bayesian analysis of data from a randomized clinical trial of early extracorporeal membrane oxygenation compared with conventional lung-protective ventilation with the option for rescue extracorporeal membrane oxygenation among patients with very severe acute respiratory distress syndrome provides information about the posterior probability of mortality benefit under a broad set of assumptions that may help inform interpretation of the study findings.

ARTICLE INFORMATION

**Accepted for Publication:** September 26, 2018.

**Published Online:** October 22, 2018. doi:10.1001/jama.2018.14276

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*Administrative, technical, or material support:* Slutsky, Combes.

**Conflict of Interest Disclosures:** Dr Goligher reports receiving travel reimbursement and speaking honoraria from Getinge outside the submitted work. Dr Jüni reports being a tier 1 Canada research chair in clinical epidemiology of chronic diseases. Dr Brodie reports serving as the cochair of the trial steering committee for the VENT-AVOID trial sponsored by ALung Technologies; he previously served on the medical advisory boards of ALung Technologies and Kadence (Johnson & Johnson), with all compensation for these activities paid to Columbia University. Dr Slutsky reports serving as a paid consultant for Maquet Critical Care, Baxter, and Novalung/Xenios. Dr Combes reports receiving study grant support from Maquet, lecture fees from Maquet and Baxter, and consulting fees from Hemovent, outside the submitted work. No other disclosures were reported.

**Funding/Support:** This work is supported by a new investigator award from the Canadian Institutes of Health Research (Drs Fan and Wijeysundera) and a merit award from the department of anesthesia at the University of Toronto (Dr Wijeysundera).

**Role of the Funder/Sponsor:** The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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