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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Venovenous Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome: A Post-Hoc Bayesian Analysis of a Randomized Clinical Trial

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Key Points (Word Count = 119)

Question

Can Bayesian analysis clarify the interpretation of clinical trial results?

Findings

In a *post hoc* Bayesian analysis of the recent EOLIA (ECMO to Rescue Acute Lung Injury) 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 <0.67 ranged between 0% to 48% given the same range of prior assumptions.

Meaning

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

Abstract (Word Count = 445)

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 recent randomized trial.

Design and Evidence

A *post hoc* Bayesian analysis of data from a randomized clinical trial (ECMO to Rescue Acute Lung Injury, EOLIA) that included 249 patients with very severe ARDS who had been randomized to receive early ECMO (n=124; mortality at 60 days, 35%) versus initial conventional lung-protective ventilation with the option for rescue ECMO (n=125, mortality at 60 days, 46%). Statistical prior distributions were specified to represent varying levels of pre-existing enthusiasm or skepticism for ECMO and by Bayesian meta-analysis of previously published studies (with downweighting to account for differences between studies). The relative risk (RR), credible interval (CrI), absolute risk reduction (ARR), and probability of clinically important mortality benefit (varying from RR<1 to RR<0.67 and ARR from ≥2% to ≥20%) were estimated with Bayesian modelling.

Findings

Combining a minimally informative prior distribution with the findings of EOLIA, the posterior probability of RR < 1 for mortality at 60 days after randomization was 96% (RR 0.78, 95% CrI 0.56-

1.04); the posterior probability of RR<0.67 was 18%, the probability of ARR≥2% was 92%, and the probability of ARR≥20% 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<1 was 99%, the probability of RR<0.67 was 8%, the probability of ARR≥2% was 97%, and the probability of ARR≥20% 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<1 was 88%, the probability of RR<0.67 was 0%, the probability of ARR≥2% was 78%, and the probability of ARR≥20% 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<1 was 99%, the probability of RR<0.67 was 48%, the probability of ARR≥2% was 98%, and the probability of ARR≥20% was 4%.

Conclusion

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

Trial Registration – this analysis was NOT registered

Introduction

The conventional frequentist approach to statistical analysis of clinical trials evaluates study hypotheses *indirectly* by estimating the probability that *data* as or more extreme than the observed treatment effect size 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 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 pre-existing 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 trial of extracorporeal membrane oxygenation (ECMO to Rescue Lung Injury in Severe ARDS—EOLIA)[7] offers an example of the value of Bayesian analysis. In this trial, the effect of early ECMO on mortality in very severe ARDS did not reach statistical significance (p=0.09 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 pre-existing 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.

Methods

EOLIA was a multicenter international randomized clinical trial designed to test the hypothesis that early venovenous ECMO reduces 60-day mortality in patients with very severe forms of ARDS

(PaO2/FiO2 < 50 mm Hg for >3 hours; or PaO2/FiO2 < 80 mm Hg for >6 hours; or pH<7.25 and PaCO2≥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).[13] 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). The trial received ethical approval from the ethics committees at all participating sites.

This article presents a previously unplanned re-analysis of the primary pre-specified 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 was established from several considerations. First, because the null hypothesis under frequentist conventions in the trial was 'no benefit' (RR=1), we estimated the probability of any mortality benefit (RR<1). Second, we deemed ARR values of 2% to be a reasonable potential minimum clinically important effect as 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,[14] an annual incidence of ARDS of 80/100,000 population,[15] and a prevalence of very severe ARDS of approximately 10% among all cases of ARDS[16]). 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<0.67 and an ARR≥20%; therefore the posterior probabilities across a range of effect sizes were computed.

Bayesian analysis represents one's prior beliefs about the plausible range of values for treatment effect as a probability density distribution. The width (variance) of this distribution represents the confidence in the treatment effect while the area under the distribution at any given value represents the probability that the treatment effect is greater than or equal to that value (see **Figure 1** for examples). Two approaches were used to develop prior 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 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 pre-existing controversy amongst experts in the field[8,17] (**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 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,[9,16] the priors were defined so as to represent enthusiastic or skeptical viewpoints with respect to (a) the probability that the true effect of ECMO on mortality is the same or greater than that used to power the trial (i.e. RR$\leq$0.67) or the effect observed in the ARDSNet trial of low tidal volume ventilation (a classic trial in the treatment of ARDS, RR$\leq$0.78)[18] and (b) the probability that ECMO would worsen mortality (i.e. 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.

Second, data-derived prior distributions were developed based on relevant studies[19-21] from a meta-analysis of ECMO for ARDS.[22] 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 non-informative priors). In effect, 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 prior studies (e.g., non-randomized design in two studies, confounding by transfer to specialist centers, suboptimal control group management), the variance of the previous studies was inflated so that patients in pre-existing studies were "downweighted" to exert less influence (i.e. 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 us to mathematically represent the uncertainty about the estimates of effect in studies given their likely differences (methodological limitations?). The effects and level of uncertainty described by the data-derived priors are represented graphically in **Figure 1B**.

Each prior distribution for the log relative risk in the trial was included in a Bayesian model which specified independent binomial sampling of the numbers of deaths in the ECMO and control groups [AU: This phrase is confusing and it is unclear if the 46% mortality in the control group was held constant or, instead, the data for the control group was resampled in some way.] and a uniform prior on the control group risk of mortality. Markov Chain Monte Carlo modelling (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 (CrI) from the median, 2.5^{th} and 97.5^{th} percentiles of the posterior distribution, and to estimate the posterior probabilities of treatment effects exceeding certain thresholds. The Gelman-Rubin statistic was used to assess convergence of all models. All analyses were conducted in R (www.r-project.org, Version 3.5.0) using *R2jags*[23] to run JAGS.[24]

Results

Bayesian Analysis Using a Minimally Informative Prior

Posterior probabilities of relative and absolute risk 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 relative risk reductions for each prior. With the non-informative

prior, the estimated median relative risk for mortality at 60 days with early ECMO was 0.78 (95% credible interval, CrI, 0.56-1.04). The posterior probability of mortality benefit with early ECMO (i.e. RR<1) was 96%, the probability of RR<0.67 was 18%. Assuming a baseline mortality risk of 46%, the probability of ARR≥2% was 92%, and the probability of ARR≥20% was 2% (**Table 3**).

Bayesian Analysis Using Reference Priors

The posterior probability of RR<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<1 was 88%, the probability of RR<0.67 was 0%, the probability of ARR≥2% was 78%, and the probability of ARR≥20% was 0%.

Bayesian Analysis Using the Data-Derived Prior

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

When the previous studies were downweighted to account for their likely differences (methodological limitations?) by up to 90%, the upper limit of the 95% credible interval for treatment effect fell below 1 and the probability of RR<1 exceeded 90% (**Figure 3**). The probability of RR<0.67 and ARR≥20% remained low across the range of downweighting (**Table 2** and **Figure 3**).

Discussion

Bayesian analysis constitutes an alternative to the conventional paradigm 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. [25] Many statisticians have advocated for the incorporation of Bayesian analysis in trial design and interpretation to complement frequentist analysis but adoption in clinical research has been limited. Recently, the United States Food & Drug Administration developed guidelines for the application of Bayesian statistics in trial design and interpretation in clinical trials of medical devices. [26] 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 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." This conclusion appropriately reflects the frequentist approach to hypothesis testing. The probability of observing an absolute mortality difference of ≥11% under the null hypothesis of no treatment effect was not sufficiently low to warrant rejection of the null hypothesis according to frequentist conventions (RR 0.76, 95% CI 0.55-1.04, p=0.09 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% confidence interval 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] while another suggested that "ECMO probably has some benefit in this context."[27]

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 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 absolute risk reduction. For an absolute risk reduction of ≥2%, the posterior probability of

benefit ranged between 78% and 98%, depending on the prior. For an absolute risk reduction of ≥20%, the posterior probability ranged between 0%-2%.

The analyses described here 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,[20] 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."[28] 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 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 absolute risk reduction of 2% as a potential threshold for clinically important treatment effect. However, this threshold may be insufficient to motivate the routine use of early ECMO. Indeed, with an absolute risk reduction 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 relative and absolute risk reductions were reported. Further investigation using decision analysis may help to define the optimal value for clinically important treatment effect.

There are challenges with Bayesian analysis. Given their significant influence on posterior probabilities, the priors must be specified to appropriately reflect the evidence available prior to the trial. Selection of priors therefore requires careful forethought. 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 archetypal considerations and on prior data.

The data-derived prior was estimated based on previous studies deemed to be of acceptable methodological quality (randomized trials and 'quasi-randomized' studies employing rigorous propensity-score techniques for analysis). Because the methodological limitations of these studies reduced confidence in their estimates of effect,[22,29] 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 heavily downweighted such that a patient in the pre-existing studies contributed much less influence in comparison to a patient enrolled in EOLIA.

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 EOLIA accordingly. One important decision is the specification of the strongly skeptical prior; this requires a judgment about the upper limit of reasonable skepticism. The strongly skeptical prior specified for this

analysis is equivalent to the information derived from a hypothetical trial of early ECMO enrolling 264 patients (6% more than EOLIA) that finds the same risk of death in treatment and control groups—as there are no studies of this magnitude published in the current ECMO era, this degree of skepticism may be difficult to justify. This prior distribution therefore appears to appropriately represents the upper limit of reasonable prior skepticism.

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 (i.e. should one apply a treatment that has a predicted probability of benefit of 70% vs. 80% vs. 90% etc.), the minimum clinically important treatment effect size, the effect on outcomes other than mortality (i.e. 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.

Bayesian posterior probabilities can also inform the question as to whether future trials are required. For example, some might propose conducting yet another randomized trial of early ECMO to confirm mortality benefit (RR<1) under frequentist conventions (i.e. $p<0.05$). 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 a randomized trial 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.[30]

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 re-analyses. First, the present analysis constitutes an unplanned *post hoc* analysis of trial data. Such analyses should generally be treated with caution (i.e., 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').[31] Several considerations, however, suggest that the present analyses are less vulnerable to these concerns. They tested the same hypothesis and analyzed the same pre-specified primary end-point as in the original publication—the pre-specified 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.[32]

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 EOLIA.[33] Empirically-derived priors might have helped to clarify the extent to which EOLIA 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.

Conclusions

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

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Conflicts of Interest Disclosures

Dr. Goligher reports receiving personal fees from Getinge outside the submitted work. Dr. Brodie is the co-chair of the Trial Steering Committee for the VENT-AVOID trial sponsored by ALung Technologies; he was previously on the medical advisory boards of ALung Technologies and Kadence (Johnson & Johnson). All compensation for these activites was paid to Columbia University. Dr. Slutsky reports personal fees from Maquet Critical Care, personal fees from Baxter, personal fees from Novalung/Xenios. Dr. Combes reports grants from Maquet, personal fees from Maquet, personal fees from Baxter, personal fees from Hemovent, outside the submitted work. The other authors had no conflicts of interest to disclose.

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Figure Legends

Figure 1. Graphical representation of reference priors (Left) and data-derived priors (Right). Each prior distribution represents a belief about the probability of differing mortality benefits (relative risks of death) with the use of early ECMO in patients with very severe acute respiratory distress syndrome. Bayesian analysis combines each prior distribution with the likelihood function of the observed treatment benefit to determine the posterior probability of treatment benefit. 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 entails that all potential values for log relative risk are approximately equally likely. The data-derived priors are based on previous studies (see text for details). To account for likely differences in previous studies, the weight (influence) of patients enrolled in these prior studies was reduced by artificially inflating the study variance (resulting in a wider prior probability density distribution).

Figure 2. Posterior probability distributions for relative risk (Panel A) and absolute risk reduction (Panel B) obtained based on the EOLIA trial results under varying prior assumptions about the benefit of early ECMO on mortality. Prior distributions (represented by the red lines) are combined with the likelihood function summarizing the treatment effect observed in the trial (green shaded region) to compute the posterior probability for the treatment effect. In each case the likelihood function, summarizing the trial data, is the same; variation in the posterior distribution arises from variation in the prior. In the case of a non-informative prior, the likelihood function and posterior distribution are identical. The median effect and credible interval are shown as the black point and line below each set of distributions. This approach allows assessment of the influence of prior enthusiasm or skepticism for early ECMO on the interpretation of the trial.

Figure 3. Posterior probabilities for a reduction in mortality with VV-ECMO in very severe ARDS given EOLIA and the results of previous studies. 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). The left panel shows the resulting credible interval for the relative risk of mortality for various levels of weighting of previous studies in proportion to the weight assigned to the EOLIA trial. The right panel shows the resulting estimated probability of a given relative risk reduction for varying weights assigned to the previous studies. EOLIA = "ECMO to Rescue Acute Lung Injury" randomized trial; CrI = credible intervals; RR = relative risk.

Table 1. Characteristics of Reference Prior Probability Distributions Representing Prior Beliefs About Mortality Benefit from ECMO

Prior belief	Assumed Median Relative Risk	Assumed Standard Deviation of Logarithm of Relative Risk	Prior Evidence Equivalent*	Probability of Treatment Effect Equal to or Greater Than Specified Threshold				Rationale for Specifying Distribution Characteristics
				RR < 1	RR < 0.9	RR < 0.8	RR < 0.7	
Non-informative	1.0	10	Equivalent to essentially no prior data	50%	50%	49%	49%	All possible values for treatment effect for log RR [author – correct?] are equally likely
Strongly enthusiastic	0.67	0.25	Equivalent to a previous RCT enrolling 100 patients finding a 33% relative risk reduction	95%	89%	77%	58%	Probability of observing a treatment effect equal to or greater than that assumed in EOLIA 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 a 22% relative risk reduction	95%	83%	57%	24%	Probability of observing a treatment effect equal to or greater than 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 a 0% relative risk reduction	50%	33%	18%	7%	Probability of observing a treatment effect equal to or greater than that assumed in EOLIA 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% relative risk reduction	50%	24%	7%	1%	Probability of observing a treatment effect equal to or greater than that observed in the ARDSNet lower tidal volume trial (RR=0.78) is 5%

RR = relative risk, EOLIA = ECMO to Rescue Acute Lung Injury trial, ARDSNet = NIH/NHLBI ARDS Network, RCT = randomized controlled trial

*"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 randomized trial required to generate the level of informative influence on posterior probability specified by the reference prior relative to the size of the EOLIA trial

Table 2. Probability of treatment effects estimated by Bayesian analysis using varying distributions to describe prior beliefs

Prior belief		Posterior Median Relative Risk (95% Credible Interval)	Posterior Probability that True Relative Risk Is Less Than or Equal to Specified Threshold			
			RR < 1	RR < 0.9	RR < 0.8	RR < 0.67
Reference Prior Distributions	Non-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[a] of previous studies	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%

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 compared to the current trial.

Table 3. Probability that early ECMO reduces mortality by a proposed minimum clinically important difference according to varying possible baseline mortality rates in patients with very severe ARDS

Prior belief		Posterior Median Absolute Risk Reduction (95% Credible Interval)	Posterior Probability that Absolute Risk Reduction[a] is Greater Than or Equal to Specified Threshold					
			2%	4%	6%	8%	10%	20%
Reference Prior Distributions	Non-informative	-10.6% (-20.0% - 1.8%)	92%	86%	78%	67%	53%	2%
	Strongly enthusiastic	-12.0% (-19.9% - -2.1%)	98%	95%	89%	79%	65%	2%
	Moderately enthusiastic	-10.4% (-17.2% - -2.0%)	97%	93%	85%	71%	51%	0%
	Skeptical	-7.8% (-16.5% - 3.4%	86%	76%	62%	47%	30%	0%
	Strongly skeptical	-5.6% (-13.3% – 4.1%)	78%	63%	45%	26%	13%	0%
Data-Derived Prior Distribution	No downweighting of previous studies	-13.6% (-20.5% - -2.9%)	98%	96%	93%	88%	79%	4%
	50% downweighting of previous studies	-12.8% (-20.4% - -1.9%)	97%	95%	91%	83%	72%	3%
	75% downweighting of previous studies	-12.1% (-20.3% - -1.1%)	97%	93%	88%	79%	66%	3%

ECMO = extracorporeal membrane oxygenation; ARDS = acute respiratory distress syndrome

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

538 Figure 1
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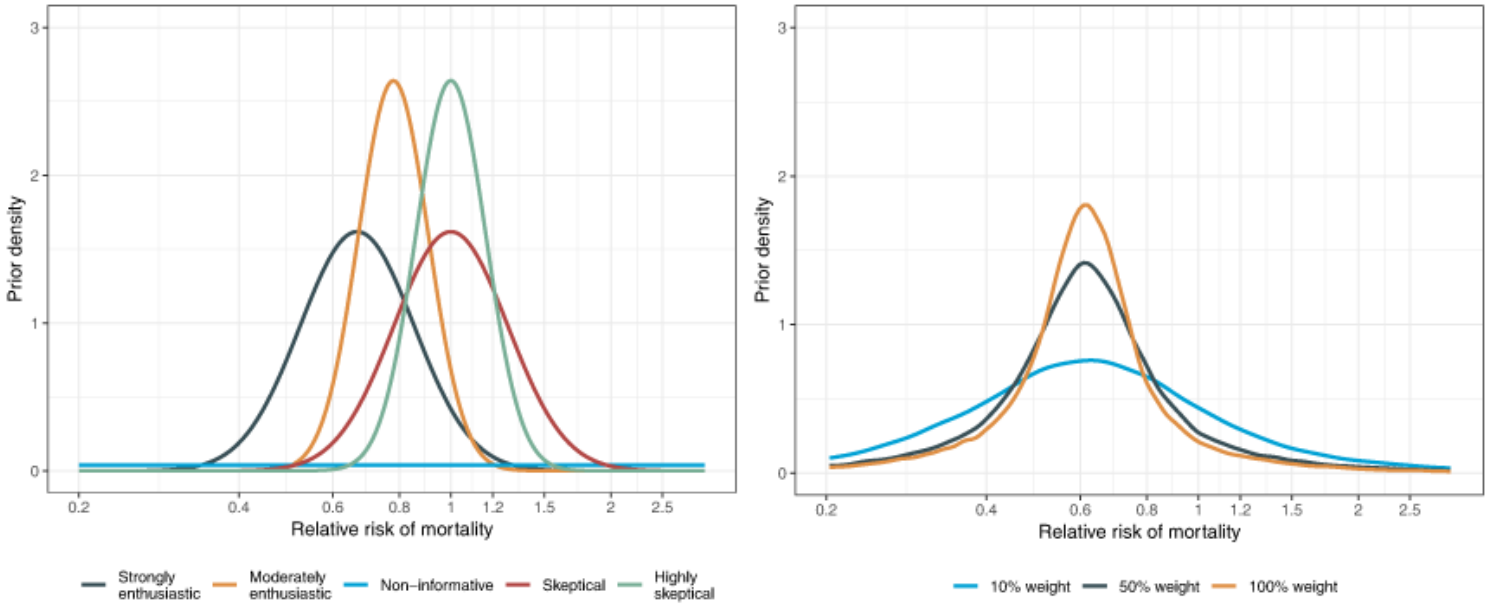
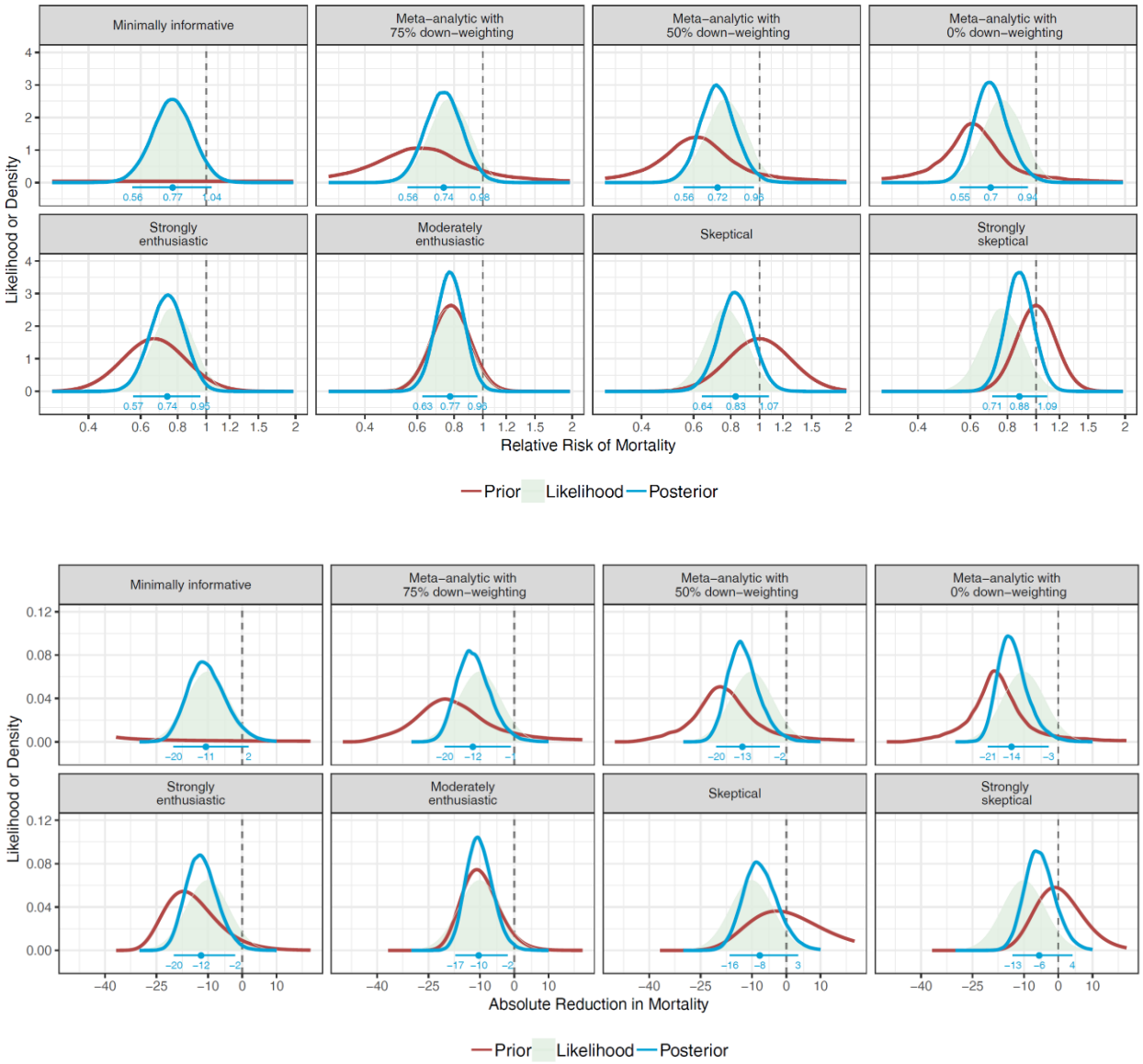


Figure 2


Minimally informative
Meta−analytic with 75% down−weighting
Meta−analytic with 50% down−weighting
Meta−analytic with 0% down−weighting
Strongly enthusiastic
Moderately enthusiastic
Skeptical
Strongly skeptical
Likelihood or Density
Relative Risk of Mortality
Absolute Reduction in Mortality
Prior
Likelihood
Posterior

571 Figure 3
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