



HAL
open science

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

Ewan C Goligher, George Tomlinson, David Hajage, Duminda N Wijeyesundera, Eddy Fan, Peter Jüni, Daniel Brodie, Arthur Slutsky, Alain Combes

► **To cite this version:**

Ewan C Goligher, George Tomlinson, David Hajage, Duminda N Wijeyesundera, Eddy Fan, et al.. 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. JAMA Ophthalmology, 2018, 320 (21), pp.2251. 10.1001/jama.2018.14276 . hal-01973355

HAL Id: hal-01973355

<https://hal.sorbonne-universite.fr/hal-01973355>

Submitted on 8 Jan 2019

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

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

3

4 Ewan C. Goligher MD PhD^{1,2,3}

5 George Tomlinson PhD^{2,3,4}

6 David Hajage PhD⁵

7 Duminda N. Wijeyesundera MD PhD^{4,6,7,8}

8 Eddy Fan MD PhD^{1,2,4}

9 Peter Jüni MD^{4,8}

10 Daniel Brodie MD^{9,10}

11 Arthur S. Slutsky MD^{1,11}

12 Alain Combes MD PhD^{12,13}

13

14 **Institutional Affiliations**

- 15 1. Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, Canada
- 16 2. Department of Medicine, University Health Network, Toronto, Canada
- 17 3. Toronto General Hospital Research Institute, Toronto, Canada
- 18 4. Institute for Health Policy, Management, and Evaluation, University of Toronto, Toronto, Canada
- 19 5. Sorbonne Université, Département Biostatistique Santé Publique et Information Médicale, Unité
- 20 de Recherche Clinique, Centre de Pharmacoépidémiologie (Cephepi), AP-HP, Hôpitaux
- 21 Universitaires Pitié Salpêtrière – Charles Foix, F-75013 Paris, France
- 22 6. Department of Anesthesia, University of Toronto, Toronto, Canada
- 23 7. Department of Anesthesia and Pain Management, Toronto General Hospital, Toronto, Canada
- 24 8. Applied Health Research Centre of the Li Ka Shing Knowledge Institute, St. Michael's Hospital,
- 25 Department of Medicine, University of Toronto, Toronto, Canada

- 26 9. Division of Pulmonary, Allergy, and Critical Care Medicine, Columbia University Medical
27 Center, New York, NY
- 28 10. New York-Presbyterian Hospital, New York, NY
- 29 11. Keenan Centre for Biomedical Research, Li Ka Shing Knowledge Institute, St. Michael's
30 Hospital, Toronto, Canada
- 31 12. Sorbonne Université INSERM Unité Mixte de Recherche (UMRS) 1166, Institute of
32 Cardiometabolism and Nutrition, Paris, France
- 33 13. Service de Médecine Intensive-Réanimation, Institute de Cardiologie, Assistance Publique-
34 Hôpitaux de Paris (APHP) Hôpital Pitié-Salpêtrière, Paris, France

35

36 **Date of Revision:**

37 September 20, 2018

38

39 **Word Count:**

40 3,560

41

42 **Corresponding Author:**

43 Dr. Ewan Goligher

44 Toronto General Hospital

45 585 University Ave.

46 Peter Munk Building, 11th Floor Room 192

47 Toronto ON, M5G 2N2

48 +1 (416) 340-4800 ext. 6810

49 ewan.goligher@utoronto.ca

50

51

52 **Key Points** (Word Count = 119)

53 *Question*

54 Can Bayesian analysis clarify the interpretation of clinical trial results?

55

56 *Findings*

57 In a *post hoc* Bayesian analysis of the recent EOLIA (ECMO to Rescue Acute Lung Injury) trial, the
58 posterior probability of mortality benefit (relative risk < 1) ranged between 88% and 99% given a range of
59 prior assumptions reflecting varying degrees of skepticism and enthusiasm regarding previous evidence
60 for the benefit of ECMO. Probabilities varied according to the definition of minimum clinically important
61 mortality benefit; for example, the posterior probability of relative risk < 0.67 ranged between 0% to 48%
62 given the same range of prior assumptions.

63

64 *Meaning*

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

67 **Abstract** (Word Count = 445)

68 *Importance*

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

73

74 *Objective*

75 To demonstrate the potential utility of Bayesian analyses by estimating the posterior probability, under
76 various assumptions, that early ECMO was associated with reduced mortality in patients with very severe
77 ARDS in a recent randomized trial.

78

79 *Design and Evidence*

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

89

90 *Findings*

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

93 1.04); the posterior probability of $RR < 0.67$ was 18%, the probability of $ARR \geq 2\%$ was 92%, and the
94 probability of $ARR \geq 20\%$ was 2%. With a moderately enthusiastic prior, equivalent to information from a
95 trial of 264 patients with an RR of 0.78, the estimated RR was 0.78 (95% CrI 0.63-0.96), the probability
96 of $RR < 1$ was 99%, the probability of $RR < 0.67$ was 8%, the probability of $ARR \geq 2\%$ was 97%, and the
97 probability of $ARR \geq 20\%$ was 0%. With a strongly skeptical prior, equivalent to information from a trial
98 of 264 patients with an RR of 1.0, the estimated RR was 0.88 (95% CrI 0.71-1.09), the probability of
99 $RR < 1$ was 88%, the probability of $RR < 0.67$ was 0%, the probability of $ARR \geq 2\%$ was 78%, and the
100 probability of $ARR \geq 20\%$ was 0%. If the prior was informed by previous studies, the estimated RR was
101 0.71 (95% CrI 0.55-0.94), the probability of $RR < 1$ was 99%, the probability of $RR < 0.67$ was 48%, the
102 probability of $ARR \geq 2\%$ was 98%, and the probability of $ARR \geq 20\%$ was 4%.

103

104 *Conclusion*

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

109

110 *Trial Registration – this analysis was NOT registered*

111

112 **Introduction**

113 The conventional frequentist approach to statistical analysis of clinical trials evaluates study
114 hypotheses *indirectly* by estimating the probability that *data* as or more extreme than the observed
115 treatment effect size would be obtained if the null hypothesis (which generally assumes that there is no
116 treatment effect) was true—the goal of frequentist analysis is to determine whether the evidence leads one
117 to confidently reject the null hypothesis. In Bayesian analysis, information available prior to the trial
118 about plausible range of values of the treatment effect (represented as a probability distribution) is
119 updated by the data collected in the trial to produce a revised estimate of the plausible range of values of
120 the treatment effect.¹ Bayesian analysis informs clinical decisions by *directly* estimating the probability of
121 a hypothesized treatment effect given the observed data.^{2,3} In addition, because information about
122 treatment effect from pre-existing clinical and biological evidence is formally incorporated into statistical
123 evaluation, Bayesian methods explicitly quantify the otherwise implicit influence of clinical judgment and
124 prior beliefs on the interpretation of trial results.⁴⁻⁶

125 A recent randomized trial of extracorporeal membrane oxygenation (ECMO to Rescue Lung Injury
126 in Severe ARDS—EOLIA)⁷ offers an example of the value of Bayesian analysis. In this trial, the effect of
127 early ECMO on mortality in very severe ARDS did not reach statistical significance (p=0.09 in the
128 primary analysis). However, the clinically important point estimate of the absolute risk difference (11%),
129 the near statistical significance of the effect despite early stopping for futility, and the wide divergence of
130 pre-existing views regarding the benefit of ECMO^{8,9} (due in part to differences between prior studies and
131 their potential methodological limitations) have made interpretation of the trial controversial.¹⁰⁻¹² In this
132 Special Communication, a *post hoc* Bayesian analysis of this trial demonstrating the potential utility of
133 the Bayesian approach is presented.

134

135 **Methods**

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

138 (PaO₂/FiO₂ < 50 mm Hg for >3 hours; or PaO₂/FiO₂ < 80 mm Hg for >6 hours; or pH<7.25 and
139 PaCO₂≥60 mm Hg with a maximum plateau pressure of 32 cm H₂O and respiratory rate set at 35 breaths
140 per minute for ≥6 hours).¹³ The trial was designed to detect a decrease in mortality risk from 60% to 40%
141 (absolute risk reduction [ARR] of 20%, relative risk [RR] of 0.67). The trial received ethical approval
142 from the ethics committees at all participating sites.

143 This article presents a previously unplanned re-analysis of the primary pre-specified end-point
144 conducted using Bayesian methods. The aim was to estimate the posterior probabilities that the treatment
145 effect exceeded a range of potential values for the minimum clinically important treatment effect (RR<1,
146 RR<0.9, RR<0.8, RR<0.67; and ARR≥2%, ARR≥4%, ARR≥6%, ARR≥8%, ARR≥10%, and ARR≥20%
147 assuming a baseline mortality risk of 46% based on the EOLIA control group). This range of possible
148 values for the minimum clinically important treatment effect was established from several considerations.
149 First, because the null hypothesis under frequentist conventions in the trial was ‘no benefit’ (RR=1), we
150 estimated the probability of any mortality benefit (RR<1). Second, we deemed ARR values of 2% to be a
151 reasonable potential minimum clinically important effect as this would be equivalent to an estimated 500
152 lives saved every year in the United States (assuming approximately 25,000 cases of very severe ARDS
153 annually in the United States based on a population of 328 million persons,¹⁴ an annual incidence of
154 ARDS of 80/100,000 population,¹⁵ and a prevalence of very severe ARDS of approximately 10% among
155 all cases of ARDS¹⁶). However, arguments can be made supporting a lower RR or larger ARR as a
156 minimal clinically important difference, and the trial was designed to detect an RR<0.67 and an
157 ARR≥20%; therefore the posterior probabilities across a range of effect sizes were computed.

158 Bayesian analysis represents one’s prior beliefs about the plausible range of values for treatment
159 effect as a probability density distribution. The width (variance) of this distribution represents the
160 confidence in the treatment effect while the area under the distribution at any given value represents the
161 probability that the treatment effect is greater than or equal to that value (see **Figure 1** for examples).
162 Two approaches were used to develop prior statistical priors for this analysis. First, priors were used to
163 reflect varying degrees of enthusiasm and skepticism for the benefit of ECMO before the trial. A

164 minimally informative prior (which regards all possible log-relative risk values to be equally likely) was
165 used to produce results essentially dependent on data from the trial alone; this prior adds minimal
166 information to the trial in calculating posterior probabilities.

167 A range of reference priors were defined to represent “strongly enthusiastic”, “moderately
168 enthusiastic”, “skeptical”, and “strongly skeptical” archetypes of prior belief about the probability of
169 benefit from early ECMO consistent with pre-existing controversy amongst experts in the field^{8,17} (**Table**
170 **1**). Each prior distribution was characterized by a different assumed value for median RR (the value for
171 RR that an enthusiast or skeptic would assume to have a 50% probability of obtaining) and a different
172 width (variance, representing the magnitude of uncertainty about the plausible range of values for
173 treatment effect). To aid in understanding the strength of the enthusiasm or skepticism represented by
174 these theoretical priors, the sample size and observed RR were computed for a hypothetical clinical trial
175 achieving the same level of certainty in the treatment effect as each prior. This sample size was computed
176 by comparing the variance of each prior distribution to the variance of the log-relative risk observed in the
177 trial (**Table 1**).

178 In accordance with previously published recommendations,^{9,16} the priors were defined so as to
179 represent enthusiastic or skeptical viewpoints with respect to (a) the probability that the true effect of
180 ECMO on mortality is the same or greater than that used to power the trial (i.e. $RR \leq 0.67$) or the effect
181 observed in the ARDSNet trial of low tidal volume ventilation (a classic trial in the treatment of ARDS,
182 $RR \leq 0.78$)¹⁸ and (b) the probability that ECMO would worsen mortality (i.e. $RR > 1$). Reference priors
183 specified on this basis are described in detail in **Table 1**. **Figure 1A** depicts the probability density
184 distribution for RR specified by each reference prior distribution.

185 Second, data-derived prior distributions were developed based on relevant studies¹⁹⁻²¹ from a meta-
186 analysis of ECMO for ARDS.²² The treatment effects in these previous studies were combined with the
187 observed data from this trial in a Bayesian hierarchical random effects model (that itself used non-
188 informative priors). In effect, the previous studies generated a prior for what the treatment effect in the
189 “next” study would be, a prior that is combined with data from this trial to produce an updated

190 distribution of the estimated treatment effect after this trial. To reflect concerns about possible differences
191 between the current and prior studies (e.g., non-randomized design in two studies, confounding by
192 transfer to specialist centers, suboptimal control group management), the variance of the previous studies
193 was inflated so that patients in pre-existing studies were “downweighted” to exert less influence (i.e.
194 received less weight in the analysis) on the pooled estimate of effect. Downweighting was applied to
195 varying degrees so that patients in previous studies exerted between 0% and 100% of the weight of
196 patients enrolled in the trial. It allowed us to mathematically represent the uncertainty about the estimates
197 of effect in studies given their likely differences (methodological limitations?). The effects and level of
198 uncertainty described by the data-derived priors are represented graphically in **Figure 1B**.

199 Each prior distribution for the log relative risk in the trial was included in a Bayesian model which
200 specified independent binomial sampling of the numbers of deaths in the ECMO and control groups [AU:
201 This phrase is confusing and it is unclear if the 46% mortality in the control group was held
202 constant or, instead, the data for the control group was resampled in some way.] and a uniform
203 prior on the control group risk of mortality. Markov Chain Monte Carlo modelling (with 3 chains, 20,000
204 iterations burn-in and 20,000 saved iterations per chain) was used to derive treatment effect estimates and
205 95% credible intervals (CrI) from the median, 2.5th and 97.5th percentiles of the posterior distribution, and
206 to estimate the posterior probabilities of treatment effects exceeding certain thresholds. The Gelman-
207 Rubin statistic was used to assess convergence of all models. All analyses were conducted in R (www.r-
208 project.org, Version 3.5.0) using *R2jags*²³ to run JAGS.²⁴

209

210 **Results**

211 *Bayesian Analysis Using a Minimally Informative Prior*

212 Posterior probabilities of relative and absolute risk reductions in mortality for a range of priors are
213 shown in **Table 2** and **Table 3**. **Figure 2** presents both the likelihood function for the trial and the
214 posterior probability distribution for relative risk reductions for each prior. With the non-informative

215 prior, the estimated median relative risk for mortality at 60 days with early ECMO was 0.78 (95%
216 credible interval, CrI, 0.56-1.04). The posterior probability of mortality benefit with early ECMO (i.e.
217 $RR < 1$) was 96%, the probability of $RR < 0.67$ was 18%. Assuming a baseline mortality risk of 46%, the
218 probability of $ARR \geq 2\%$ was 92%, and the probability of $ARR \geq 20\%$ was 2% (**Table 3**).

219

220 *Bayesian Analysis Using Reference Priors*

221 The posterior probability of $RR < 1$ exceeded 90% across the strongly enthusiastic, moderately
222 enthusiastic, and skeptical priors (**Table 2, Figure 2**). In the most extreme case of a strongly skeptical
223 prior the estimated RR was 0.88 (95% CrI 0.71-1.09), the posterior probability of $RR < 1$ was 88%, the
224 probability of $RR < 0.67$ was 0%, the probability of $ARR \geq 2\%$ was 78%, and the probability of $ARR \geq 20\%$
225 was 0%.

226

227 *Bayesian Analysis Using the Data-Derived Prior*

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

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

236

237 **Discussion**

238 Bayesian analysis constitutes an alternative to the conventional paradigm for the statistical
239 evaluation of medical hypotheses. Rather than estimating the probability of the *data* given the hypothesis,
240 it aims to estimate the probability of the *hypothesis* given the data. Statisticians have long identified either

241 as “Bayesians” or as “frequentists”;² the debate turns in part on the role of deductive vs. inductive
242 inference in scientific reasoning.²⁵ Many statisticians have advocated for the incorporation of Bayesian
243 analysis in trial design and interpretation to complement frequentist analysis but adoption in clinical
244 research has been limited. Recently, the United States Food & Drug Administration developed guidelines
245 for the application of Bayesian statistics in trial design and interpretation in clinical trials of medical
246 devices.²⁶ Bayesian analysis may suggest differing conclusions from frequentist analysis, particularly
247 when observed effect sizes are relatively large but statistical power is relatively low.³

248 In the original description of the trial, the investigators concluded that “early application of ECMO
249 was not associated with mortality at 60 days that was significantly lower than that in the control group.”
250 This conclusion appropriately reflects the frequentist approach to hypothesis testing. The probability of
251 observing an absolute mortality difference of $\geq 11\%$ under the null hypothesis of no treatment effect was
252 not sufficiently low to warrant rejection of the null hypothesis according to frequentist conventions (RR
253 0.76, 95% CI 0.55-1.04, $p=0.09$ in the primary analysis). This conclusion may be at variance with clinical
254 and scientific intuition as it discounts altogether the clinically relevant effect size and a 95% confidence
255 interval that lies mostly below 1. The difficulty of interpreting the results of this frequentist analysis was
256 immediately evident with one editorial concluding that “the routine use of ECMO in patients with severe
257 ARDS is not superior to the use of ECMO as a rescue maneuver”¹¹ while another suggested that “ECMO
258 probably has some benefit in this context.”²⁷

259 The statement that ECMO probably has some benefit is an intuitive expression of the Bayesian
260 approach to data analysis. The Bayesian framework aims to define the probability of a desired treatment
261 effect rather than to rule out the absence of treatment effect. Bayesian analysis of the EOLIA trial
262 demonstrates that across a range of prior assumptions about the probability of benefit from early ECMO,
263 the posterior probability of any mortality benefit ($RR < 1$) with early ECMO is high, ranging between 88%
264 to 99%. The influence of priors on the posterior probability varied with the definition of treatment effect,
265 particularly for absolute risk reduction. For an absolute risk reduction of $\geq 2\%$, the posterior probability of

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

268 The analyses described here highlight several advantages of the Bayesian framework. First, the use
269 of statistical priors permits the wide spectrum of opinion within the clinical community regarding any
270 treatment to be formally incorporated in the analysis. This is particularly important with ECMO. In a
271 Bayesian analysis of a previous clinical trial of ECMO in children published in 1989,²⁰ Kass and
272 Greenhouse observed that “diverse opinions among knowledgeable and thoughtful observers arise
273 because (...) different people attach different degrees of importance to various pieces of information
274 concerning the merits of the treatment.”²⁸ By incorporating these varying background beliefs as priors,
275 Bayesian analysis can quantify the overall strength of evidence in support of a hypothesis, complementing
276 conventional frequentist approaches to hypothesis testing in clinical trials.

277 Second, Bayesian methods directly estimate the probability that the treatment effect is larger than a
278 clinically important threshold, given prior assumptions; such information may be more directly
279 informative to clinicians and patients or families wrestling with complex treatment decisions than
280 probabilities of observing data more extreme than the observed data if there is no real treatment effect
281 quantified by frequentist p-values. The probabilistic results of Bayesian analysis naturally align with the
282 thought processes of clinicians making treatment decisions at the bedside where the probabilities of
283 various competing benefits and harms must be weighed.

284 Third, by representing what is known about the treatment effect through a probability distribution,
285 Bayesian analysis allows the probabilities for different magnitudes of treatment effect to be estimated. For
286 the purposes of analysis, we defined an absolute risk reduction of 2% as a potential threshold for
287 clinically important treatment effect. However, this threshold may be insufficient to motivate the routine
288 use of early ECMO. Indeed, with an absolute risk reduction threshold of 20%, the posterior probability
289 was 2%. Various factors must be weighed in defining the minimum clinically important effect: the
290 baseline risk of the outcomes, the relevance of the outcome under study, the resources and expertise
291 required to deliver the intervention, the risk of treatment-related adverse effects, and the effect on other

292 clinical outcomes. Given uncertainty over this value, posterior probabilities for a range of relative and
293 absolute risk reductions were reported. Further investigation using decision analysis may help to define
294 the optimal value for clinically important treatment effect.

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

303 The data-derived prior was estimated based on previous studies deemed to be of acceptable
304 methodological quality (randomized trials and ‘quasi-randomized’ studies employing rigorous propensity-
305 score techniques for analysis). Because the methodological limitations of these studies reduced
306 confidence in their estimates of effect,^{22,29} the weight of these studies was reduced in the Bayesian
307 hierarchical model to render them less informative in the construction of the prior. Reassuringly, the
308 probability of treatment benefit remained high even when these studies were heavily downweighted such
309 that a patient in the pre-existing studies contributed much less influence in comparison to a patient
310 enrolled in EOLIA.

311 Reference priors were specified based on previous recommendations for establishing representative
312 levels of enthusiasm and skepticism.^{1,3} This approach permits assessment of prior probability both in
313 terms of existing clinical data and the strength of the biological plausibility. Readers should determine
314 which prior best matches their own background assessment of the prior probability of benefit from
315 ECMO in very severe ARDS and assess the posterior probability of benefit in light of EOLIA
316 accordingly. One important decision is the specification of the strongly skeptical prior; this requires a
317 judgment about the upper limit of reasonable skepticism. The strongly skeptical prior specified for this

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

323 Whether the findings of this Bayesian analysis support the routine use of early ECMO for very
324 severe ARDS remains a matter of judgment. This judgment must incorporate several considerations: the
325 distribution of prior probability, the probability of mortality benefit (level of certainty) required to
326 motivate action (i.e. should one apply a treatment that has a predicted probability of benefit of 70% vs.
327 80% vs. 90% etc.), the minimum clinically important treatment effect size, the effect on outcomes other
328 than mortality (i.e. long-term functional status, quality of life, costs, resource implications), and the risk
329 of adverse events. This is particularly important, because physicians often underestimate the risk of
330 adverse events. This complexity highlights the need for decision analyses; Bayesian posterior probability
331 distributions very naturally inform decision analysis.¹ The decision to initiate ECMO will always remain
332 complex; no clinical trial, however conclusive, can remove the role of clinical judgment in making
333 decisions about treatments. The findings of this Bayesian analysis may be helpful to inform these
334 judgments.

335 Bayesian posterior probabilities can also inform the question as to whether future trials are
336 required. For example, some might propose conducting yet another randomized trial of early ECMO to
337 confirm mortality benefit ($RR < 1$) under frequentist conventions (i.e. $p < 0.05$). The posterior probabilities
338 reported here can help to inform future discussions about the need for additional trials and whether the
339 ethical requirement for equipoise in a randomized trial can be satisfied. Decisions about the need for a
340 future trial depend on the definition of equipoise (probability of benefit sufficient to exclude equipoise)
341 and the definition of the minimum clinically important treatment effect.³⁰

342

343 Limitations

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

349 In addition, there are limitations specific to these Bayesian re-analyses. First, the present analysis
350 constitutes an unplanned *post hoc* analysis of trial data. Such analyses should generally be treated with
351 caution (i.e., regarded as hypothesis-generating only) because, among other concerns, repeated hypothesis
352 testing using different analyses increases the chance of erroneously concluding that the null hypothesis
353 can be rejected ('p-hacking').³¹ Several considerations, however, suggest that the present analyses are less
354 vulnerable to these concerns. They tested the same hypothesis and analyzed the same pre-specified
355 primary end-point as in the original publication—the pre-specified hypothesis or primary outcome were
356 not revised (generally entailed in secondary analyses). In addition, under Bayesian analysis, the risk of
357 erroneously estimating the posterior probability of treatment effect arises from incorrectly specifying the
358 priors, not from repeated estimates of this probability. The capacity to allow repeated estimates of
359 posterior probability is the basis for Bayesian adaptive trial design.³²

360 Second, because the analyses were planned after the trial was published, it was difficult to use
361 empirical methods to elicit prior beliefs about the benefit of ECMO; beliefs about benefit would
362 unavoidably be influenced by the results of EOLIA.³³ Empirically-derived priors might have helped to
363 clarify the extent to which EOLIA should modify the perceived probability of benefit. Recognizing this
364 limitation, a range of priors was specified to represent the range of potential prior beliefs about treatment
365 effect that might have been described by an empirical method.

366 Third, these analyses focused specifically on mortality and did not consider other adverse events.

367

368 **Conclusions**

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

373

374

375 **Acknowledgments**

376 Dr. Fan is supported by a New Investigator Award from the Canadian Institutes of Health
377 Research. Dr. Wijeyesundera is supported in part by a New Investigator Award from the Canadian
378 Institutes of Health Research and a Merit Award from the Department of Anesthesia at the University of
379 Toronto. Dr. Jüni is a Tier 1 Canada Research Chair in Clinical Epidemiology of Chronic Diseases. The
380 funder had no role in the design and conduct of the study; collection, management, analysis, and
381 interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the
382 manuscript for publication. Drs. Tomlinson and Goligher conducted and are responsible for the data
383 analysis. Dr. Goligher had full access to all the data in the study and takes responsibility for the integrity
384 of the data and the accuracy of the data analysis.

385

386 **Conflicts of Interest Disclosures**

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

395 **References**

- 396 1. Spiegelhalter DJ, Myles JP, Jones DR, Abrams KR. Methods in health service research. An
397 introduction to bayesian methods in health technology assessment. *BMJ*. 1999;319(7208):508-512.
- 398 2. Bland JM, Altman DG. Bayesians and frequentists. *BMJ*. 1998;317(7166):1151-1160.
- 399 3. Wijesundera DN, Austin PC, Hux JE, Beattie WS, Laupacis A. Bayesian statistical inference
400 enhances the interpretation of contemporary randomized controlled trials. *J Clin Epidemiol*.
401 2009;62(1):13-21.e15. doi:10.1016/j.jclinepi.2008.07.006.
- 402 4. Spiegelhalter DJ, Freedman LS, Parmar MK. Applying Bayesian ideas in drug development and
403 clinical trials. *Stat Med*. 1993;12(15-16):1501-11-discussion1513-7.
- 404 5. Brophy JM, Joseph L. Placing trials in context using Bayesian analysis. GUSTO revisited by
405 Reverend Bayes. *JAMA*. 1995;273(11):871-875.
- 406 6. Quintana M, Viele K, Lewis RJ. Bayesian Analysis: Using Prior Information to Interpret the
407 Results of Clinical Trials. *JAMA*. 2017;318(16):1605-1606. doi:10.1001/jama.2017.15574.
- 408 7. Combes A, Hajage D, Capellier G, et al. Extracorporeal Membrane Oxygenation for Severe Acute
409 Respiratory Distress Syndrome. *N Engl J Med*. 2018;378(21):1965-1975.
410 doi:10.1056/NEJMoa1800385.
- 411 8. Vincent J-L, Brochard LJ. Do we need randomized clinical trials in extracorporeal respiratory
412 support? We are not sure. *Intensive Care Medicine*. 2017;43(12):1869-1871. doi:10.1007/s00134-
413 017-4930-x.
- 414 9. Dalton HJ, MacLaren G. Extracorporeal membrane oxygenation in pandemic flu: insufficient
415 evidence or worth the effort? *Critical Care Medicine*. 2010;38(6):1484-1485.
416 doi:10.1097/CCM.0b013e3181e08fff.
- 417 10. Gattinoni L, Vasques F, Quintel M. Use of ECMO in ARDS: does the EOLIA trial really help?
418 *Critical care (London, England)*. 2018;22(1):171. doi:10.1186/s13054-018-2098-6.
- 419 11. Hardin CC, Hibbert K. ECMO for Severe ARDS. *N Engl J Med*. 2018;378(21):2032-2034.
420 doi:10.1056/NEJMe1802676.
- 421 12. Mi MY, Matthay MA, Morris AH. Extracorporeal Membrane Oxygenation for Severe Acute
422 Respiratory Distress Syndrome. *N Engl J Med*. 2018;379(9):884-887.
423 doi:10.1056/NEJMclde1804601.
- 424 13. Combes A, Hajage D, Capellier G, et al. Extracorporeal Membrane Oxygenation for Severe Acute
425 Respiratory Distress Syndrome. *N Engl J Med*. 2018;378(21):1965-1975.
426 doi:10.1056/NEJMoa1800385.
- 427 14. United States Census Bureau. <https://www.census.gov/popclock/>. Accessed September 10, 2018.
- 428 15. Rubenfeld GD, Caldwell E, Peabody E, et al. Incidence and outcomes of acute lung injury. *N Engl*
429 *J Med*. 2005;353(16):1685-1693. doi:10.1056/NEJMoa050333.

- 430 16. Bellani G, Laffey JG, Pham T, et al. Epidemiology, Patterns of Care, and Mortality for Patients
431 With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries. *JAMA*.
432 2016;315(8):788-800. doi:10.1001/jama.2016.0291.
- 433 17. Li X, Scales DC, Kavanagh BP. Unproven and Expensive before Proven and Cheap:
434 Extracorporeal Membrane Oxygenation versus Prone Position in Acute Respiratory Distress
435 Syndrome. *Am J Respir Crit Care Med*. 2018;197(8):991-993. doi:10.1164/rccm.201711-2216CP.
- 436 18. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung
437 injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome
438 Network. *N Engl J Med*. 2000;342(18):1301-1308. doi:10.1056/NEJM200005043421801.
- 439 19. Peek GJ, Mugford M, Tiruvoipati R, et al. Efficacy and economic assessment of conventional
440 ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory
441 failure (CESAR): a multicentre randomised controlled trial. *Lancet*. 2009;374(9698):1351-1363.
442 doi:10.1016/S0140-6736(09)61069-2.
- 443 20. Pham T, Combes A, Rozé H, et al. Extracorporeal membrane oxygenation for pandemic influenza
444 A(H1N1)-induced acute respiratory distress syndrome: a cohort study and propensity-matched
445 analysis. *Am J Respir Crit Care Med*. 2013;187(3):276-285. doi:10.1164/rccm.201205-0815OC.
- 446 21. Noah MA, Peek GJ, Finney SJ, et al. Referral to an extracorporeal membrane oxygenation center
447 and mortality among patients with severe 2009 influenza A(H1N1). *JAMA*. 2011;306(15):1659-
448 1668. doi:10.1001/jama.2011.1471.
- 449 22. Munshi L, Telesnicki T, Walkey A, Fan E. Extracorporeal life support for acute respiratory failure.
450 A systematic review and metaanalysis. *Annals ATS*. 2014;11(5):802-810.
451 doi:10.1513/AnnalsATS.201401-012OC.
- 452 23. Su YS, Yajima M. R2jags: Using R to Run "JAGS." R package version 0.5-7. *httpsCRANR-*
453 *projectorgpackageRjags*. <https://CRAN.R-project.org/package=R2jags>.
- 454 24. Plummer M. JAGS: Just another Gibbs sampler. *httpmcmc-jagssourceforgenet*. 2004. [http://mcmc-](http://mcmc-jags.sourceforge.net)
455 [jags.sourceforge.net](http://mcmc-jags.sourceforge.net).
- 456 25. Allmark P. Bayes and health care research. *Med Health Care Philos*. 2004;7(3):321-332.
- 457 26. Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials.
458 <https://www.fda.gov/MedicalDevices/ucm071072.htm>. Accessed September 10, 2018.
- 459 27. Harrington D, Drazen JM. Learning from a Trial Stopped by a Data and Safety Monitoring Board.
460 *N Engl J Med*. 2018;378(21):2031-2032. doi:10.1056/NEJMe1805123.
- 461 28. Kass RE, Greenhouse JB. [Investigating Therapies of Potentially Great Benefit: ECMO]:
462 Comment: A Bayesian Perspective. *Statist Sci*. 1989;4(4):310-317. doi:10.1214/ss/1177012386.
- 463 29. Fan E, Del Sorbo L, Goligher EC, et al. An Official American Thoracic Society/European Society
464 of Intensive Care Medicine/Society of Critical Care Medicine Clinical Practice Guideline:
465 Mechanical Ventilation in Adult Patients with Acute Respiratory Distress Syndrome. *Am J Respir*
466 *Crit Care Med*. 2017;195(9):1253-1263. doi:10.1164/rccm.201703-0548ST.

- 467 30. Lilford RJ. Ethics of clinical trials from a bayesian and decision analytic perspective: whose
468 equipoise is it anyway? *BMJ*. 2003;326(7396):980-981. doi:10.1136/bmj.326.7396.980.
- 469 31. Head ML, Holman L, Lanfear R, Kahn AT, Jennions MD. The extent and consequences of p-
470 hacking in science. *PLoS Biol*. 2015;13(3):e1002106. doi:10.1371/journal.pbio.1002106.
- 471 32. Berry DA. Bayesian clinical trials. *Nat Rev Drug Discov*. 2006;5(1):27-36. doi:10.1038/nrd1927.
- 472 33. Johnson SR, Tomlinson GA, Hawker GA, Granton JT, Feldman BM. Methods to elicit beliefs for
473 Bayesian priors: a systematic review. *J Clin Epidemiol*. 2010;63(4):355-369.
474 doi:10.1016/j.jclinepi.2009.06.003.

475

476

477 **Figure Legends**

478

479 **Figure 1.** Graphical representation of reference priors (Left) and data-derived priors (Right). Each prior
480 distribution represents a belief about the probability of differing mortality benefits (relative risks of death)
481 with the use of early ECMO in patients with very severe acute respiratory distress syndrome. Bayesian
482 analysis combines each prior distribution with the likelihood function of the observed treatment benefit to
483 determine the posterior probability of treatment benefit. A range of reference prior distributions were
484 specified in an effort to match the spectrum of belief within the clinical community about the benefit of
485 ECMO. The minimally informative prior distribution entails that all potential values for log relative risk
486 are approximately equally likely. The data-derived priors are based on previous studies (see text for
487 details). To account for likely differences in previous studies, the weight (influence) of patients enrolled
488 in these prior studies was reduced by artificially inflating the study variance (resulting in a wider prior
489 probability density distribution).

490

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

501

502 **Figure 3.** Posterior probabilities for a reduction in mortality with VV-ECMO in very severe ARDS given
503 EOLIA and the results of previous studies. Varying degrees of weight were applied to the previous
504 studies by artificially increasing the variance (width) of their probability distribution to reflect varying
505 levels of confidence in their estimates of effect given their likely differences (and potential
506 methodological limitations). The left panel shows the resulting credible interval for the relative risk of
507 mortality for various levels of weighting of previous studies in proportion to the weight assigned to the
508 EOLIA trial. The right panel shows the resulting estimated probability of a given relative risk reduction
509 for varying weights assigned to the previous studies. EOLIA = “ECMO to Rescue Acute Lung Injury”
510 randomized trial; CrI = credible intervals; RR = relative risk.

511

512 **Table 1.** Characteristics of Reference Prior Probability Distributions Representing Prior Beliefs About
 513 Mortality Benefit from ECMO
 514

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%

515 RR = relative risk, EOLIA = ECMO to Rescue Acute Lung Injury trial, ARDSNet = NIH/NHLBI ARDS
 516 Network, RCT = randomized controlled trial
 517 *”Prior evidence equivalent” communicates the level of certainty represented in each reference prior by
 518 reference to the treatment effect and sample size of a hypothetical randomized trial required to generate
 519 the level of informative influence on posterior probability specified by the reference prior relative to the
 520 size of the EOLIA trial
 521

522 **Table 2.** Probability of treatment effects estimated by Bayesian analysis using varying distributions to
 523 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%

524 RR = relative risk

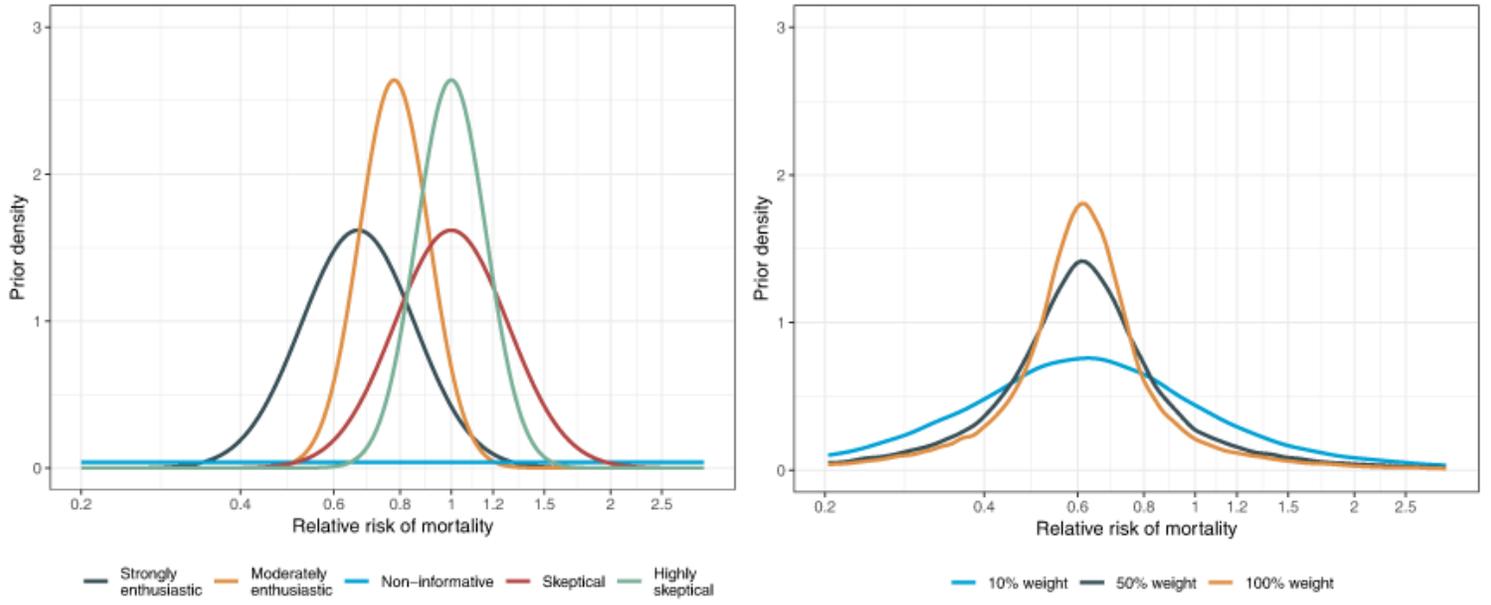
525 ^aDownweighting refers to a deliberate reduction in the influence (weight) of previous studies in the
 526 Bayesian hierarchical model by artificially increasing the variance of these studies. Downweighting
 527 provides a method of representing uncertainty about the estimates of effect in these studies given their
 528 likely differences compared to the current trial.

529 **Table 3.** Probability that early ECMO reduces mortality by a proposed minimum clinically important
 530 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%

531
 532 ECMO = extracorporeal membrane oxygenation; ARDS = acute respiratory distress syndrome
 533 ^aAbsolute risk reduction was computed assuming a baseline mortality risk of 46% (based on the mortality
 534 rate in the control group of EOLIA)
 535
 536
 537

538 Figure 1
539
540



541 Figure 2

542
543

544

545

546

547

548

549

550

551

552

553

554

555

556

557

558

559

560

561

562

563

564

565

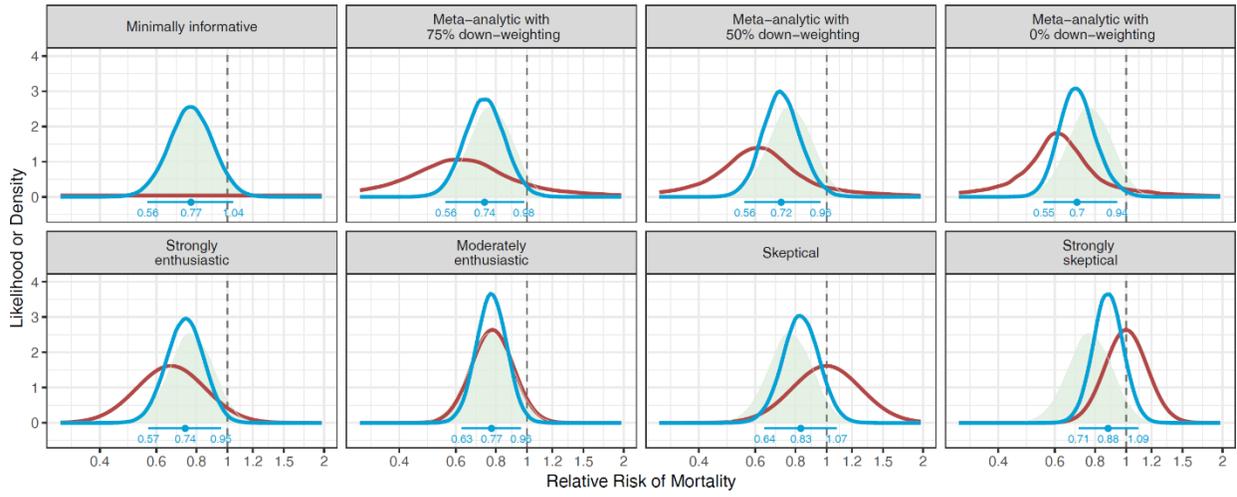
566

567

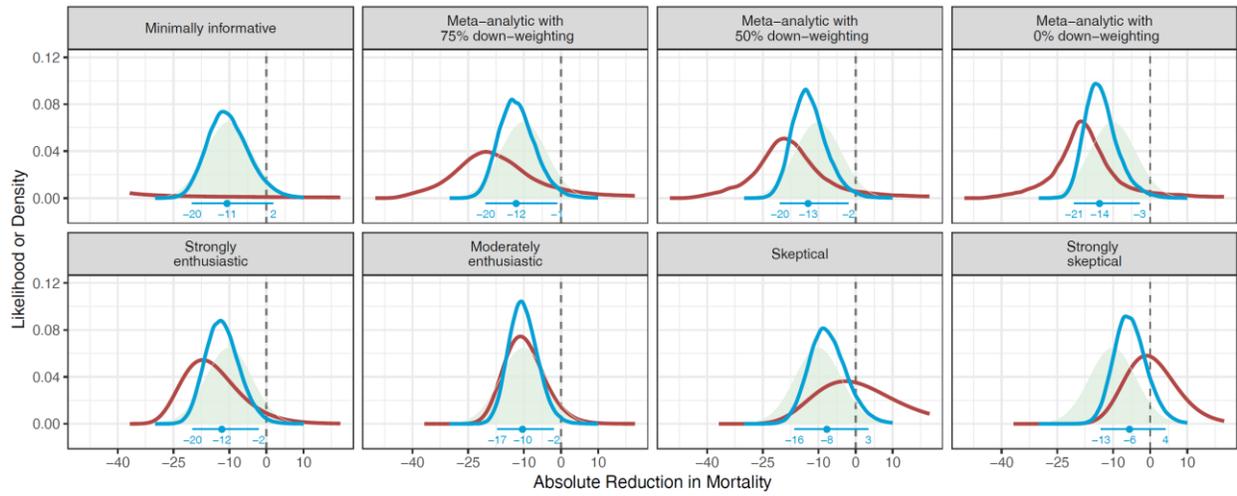
568

569

570



— Prior — Likelihood — Posterior



— Prior — Likelihood — Posterior

571 Figure 3
572
573

