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Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome

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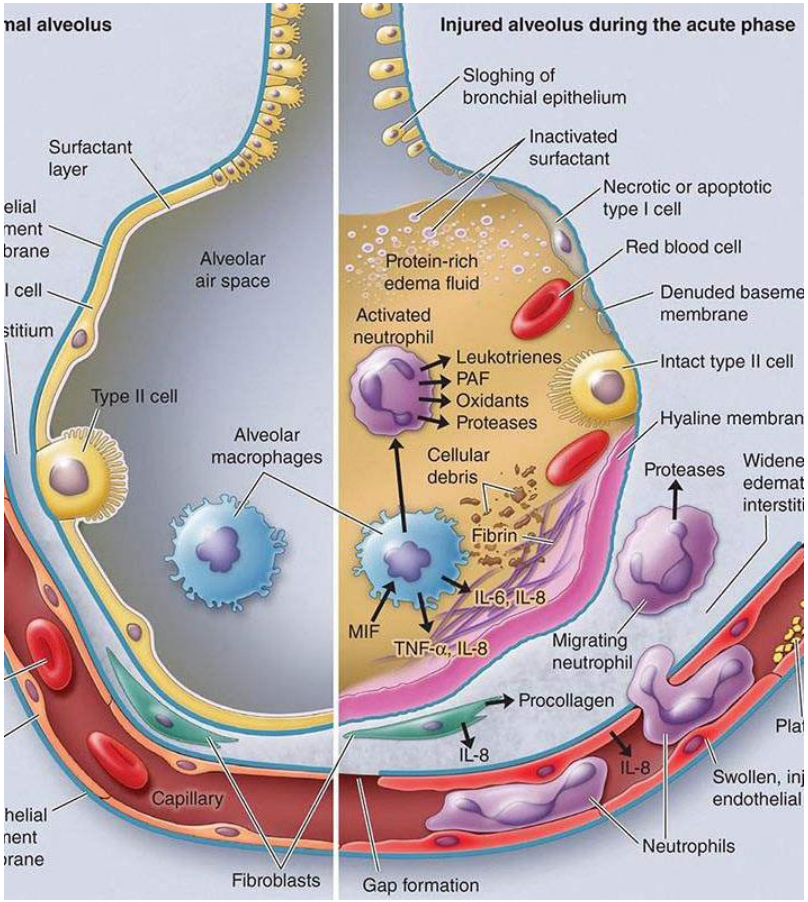
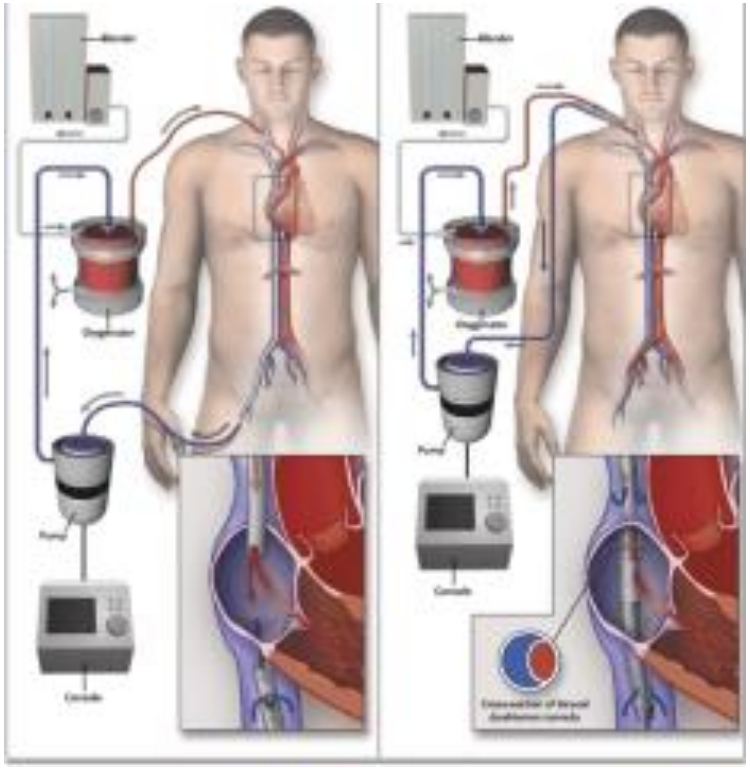
ABSTRACT

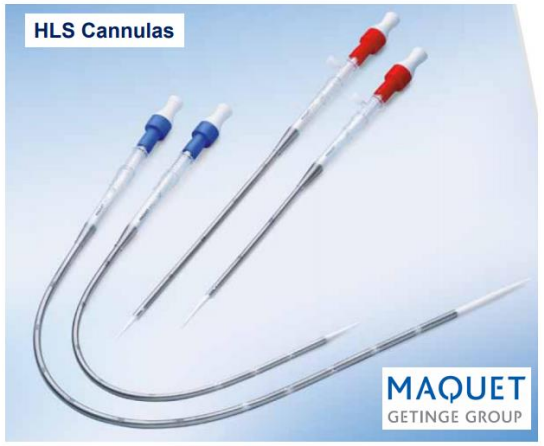
EOLIA trial

- Acute Respiratory Distress Syndrome (ARDS)
  - a rapidly progressive disease occurring in critically ill patients. The main complication in ARDS is that fluid leaks into the lungs making breathing difficult or impossible.
- ECMO to Rescue Lung Injury in Severe ARDS (EOLIA)
- EOLIA trial designed to determine the effect of
  - Early initiation of ECMO
  - In patients with the most severe forms of ARDS



ECMO and Cannulation





- Extracorporeal Membrane Oxygenation (ECMO)
- Central ECMO cannulation

Sample Size

- 60% expected 60-day mortality for controls
- 40% expected 60-day mortality with ECMO

- α=0.05; b=0.20

- Group sequential analysis every 60 inclusions
- Two-sided triangular design for early stopping
  - Superiority of ECMO
  - Predicted lack of a significant difference
  - Harm
- Maximum sample size 331 participants
- 90% probability stopping before 220 patients enrolled

- Recruitment stopped
- At the 4th planned sequential interim analysis
  - 240 patients
  - April 2017

- Lower boundary of the stopping-rule triangle
  - Crossed
  - Predicting lack of difference

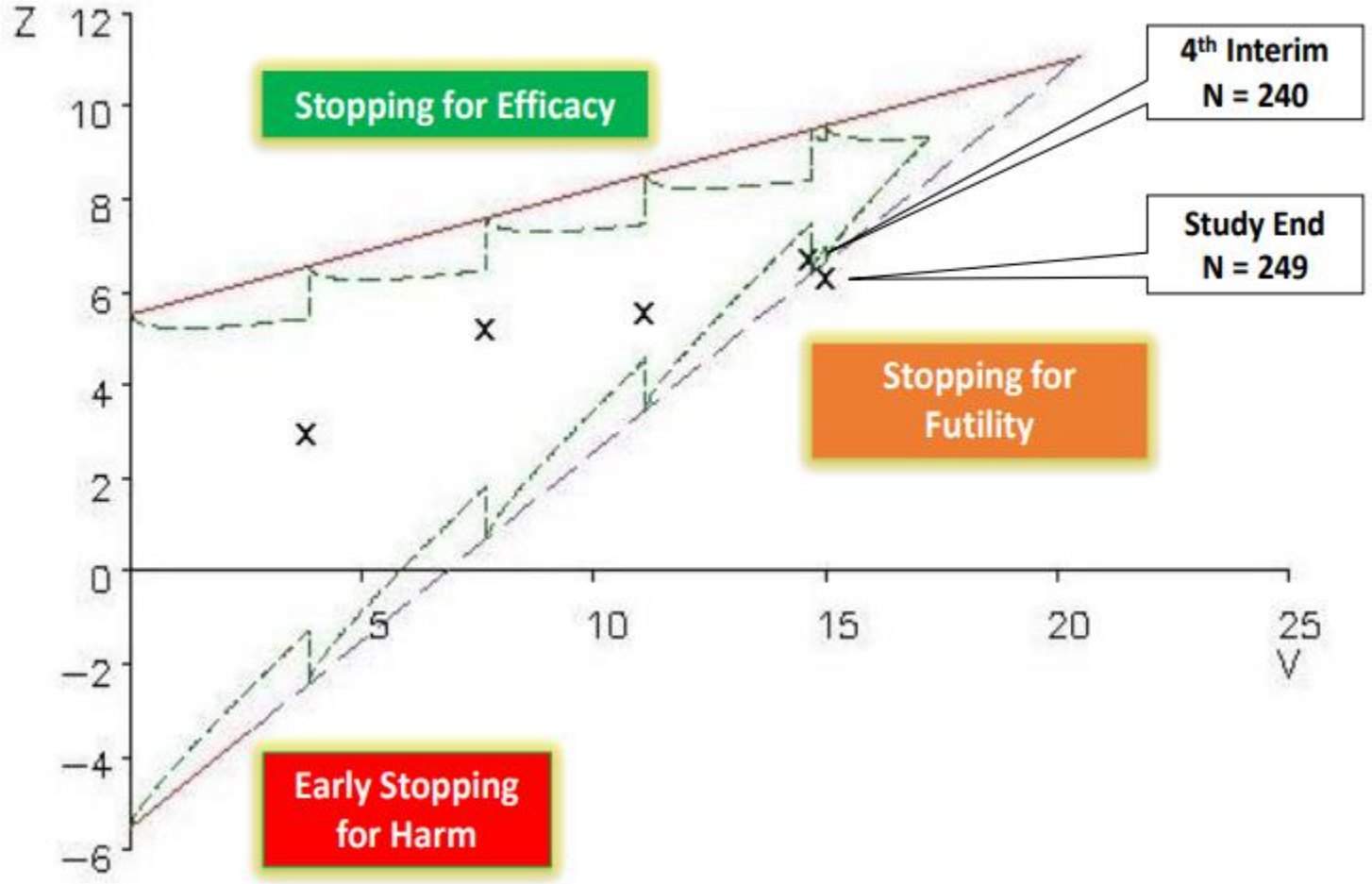
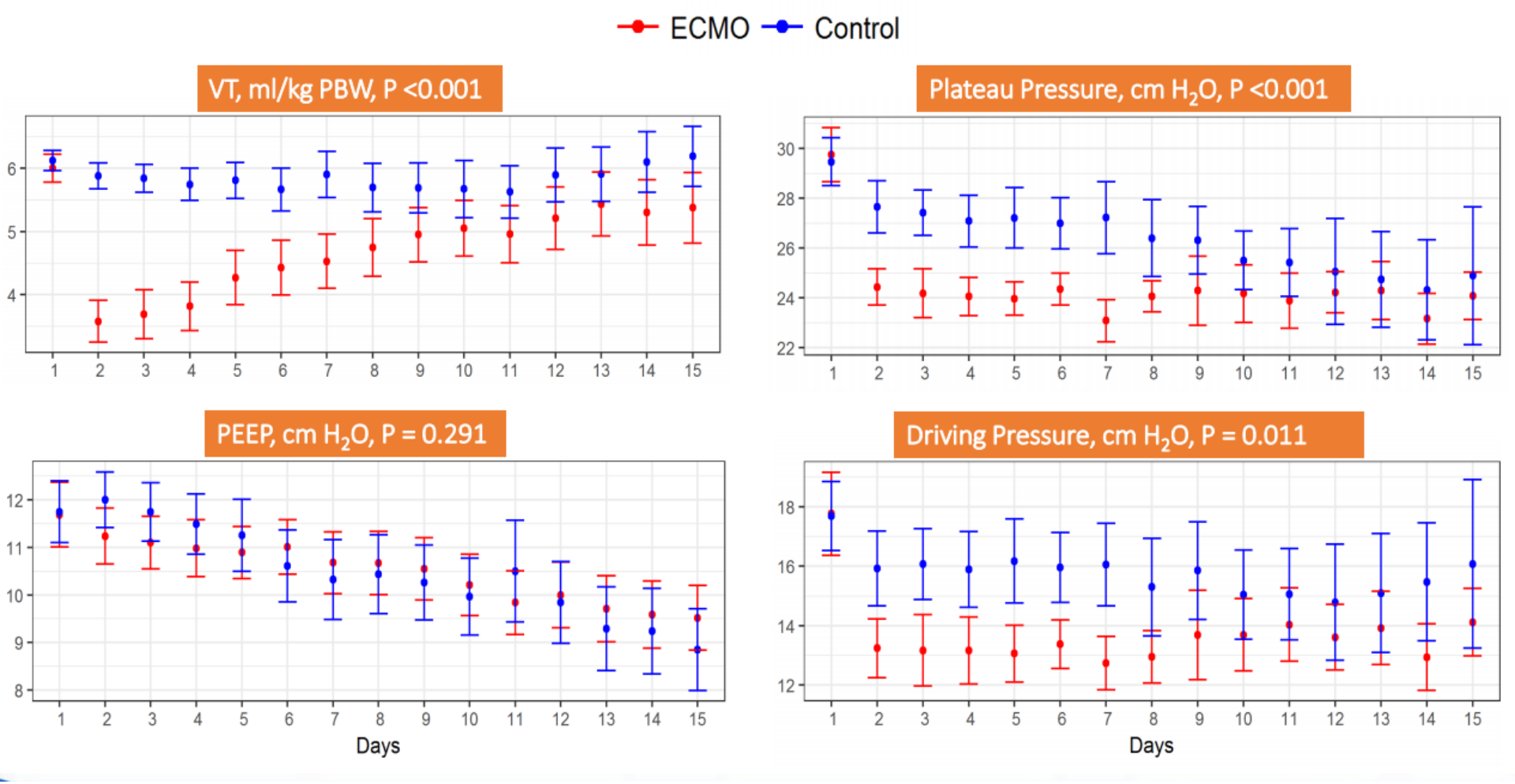
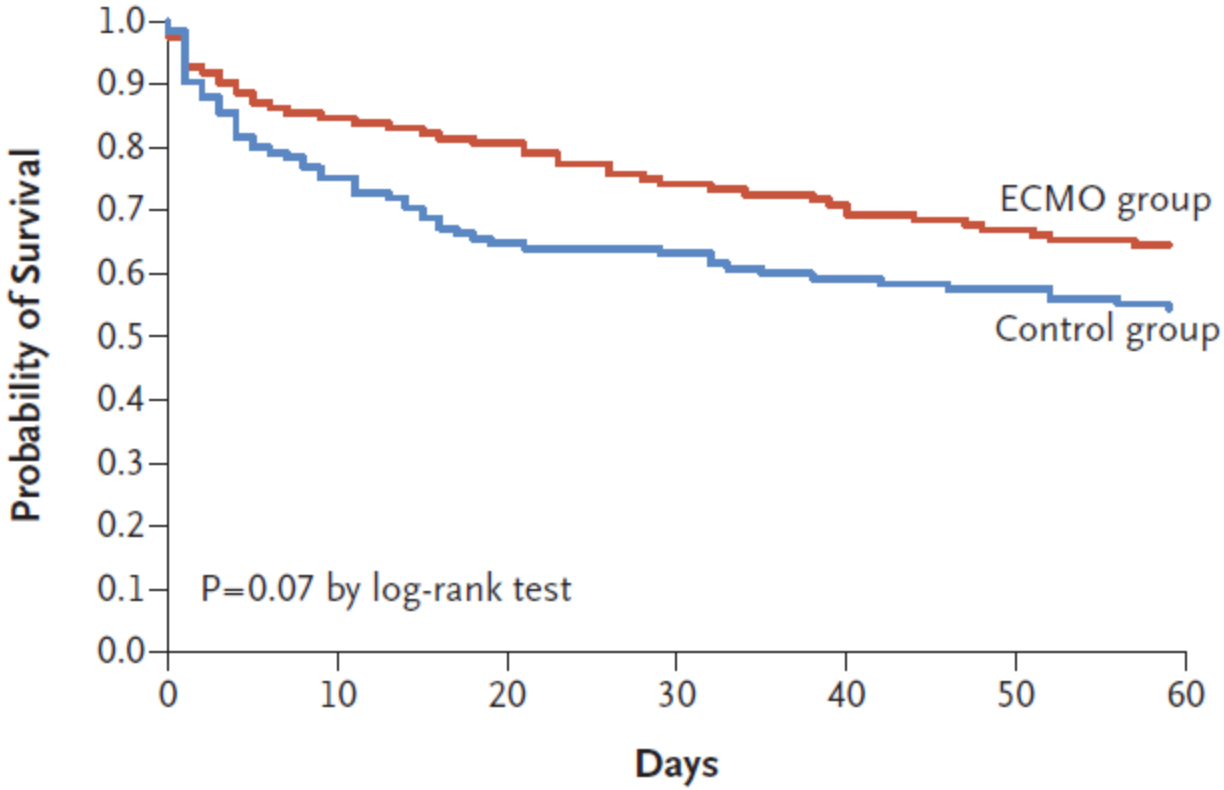

Z
12
10
8
6
4
2
0
−2
−4
−6
5
10
15
20
25
V
Stopping for Efficacy
4th Interim
N = 240
Study End
N = 249
Stopping for
Futility
Early Stopping
for Harm

Table 2. End Points.*

End Point	ECMO Group (N = 124)	Control Group (N = 125)	Relative Risk or Difference (95% CI)†	P Value
Primary end point: mortality at 60 days — no. (%)	44 (35)	57 (46)	0.76 (0.55 to 1.04)	0.09
Key secondary end point: treatment failure at 60 days — no. (%)‡	44 (35)	72 (58)	0.62 (0.47 to 0.82)	<0.001


ECMO
Control
VT, ml/kg PBW, P <0.001
Plateau Pressure, cm H2O, P <0.001
PEEP, cm H2O, P = 0.291
Driving Pressure, cm H2O, P = 0.011
Days
Days



No. at Risk							
ECMO	124	105	100	92	88	83	80
Control	125	94	81	79	74	72	69

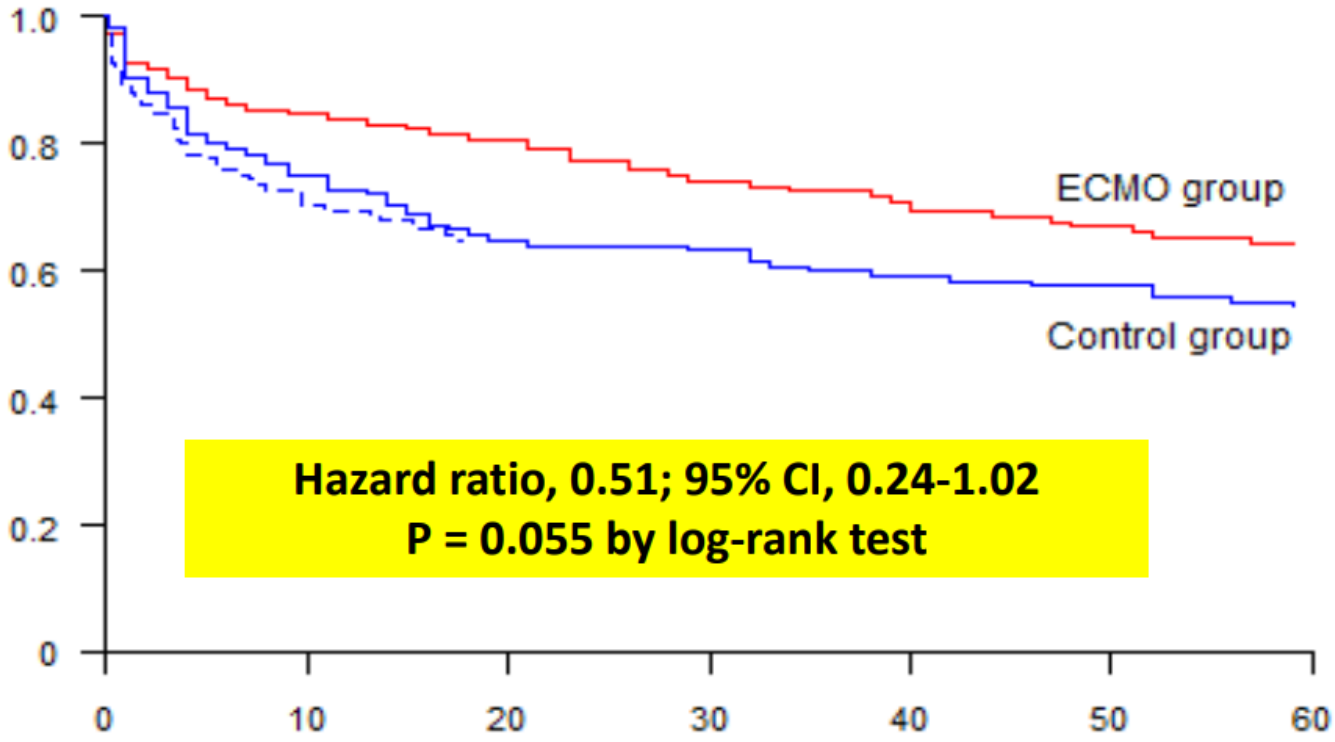
Figure 2. Kaplan–Meier Survival Estimates in the Intention-to-Treat Population during the First 60 Days of the Trial.

Crossover to ECMO in Controls

- Before crossover, of the 35 controls who had ECMO
  - 9 had cardiac arrest
  - 7 had severe right heart failure
  - 11 developed renal failure requiring dialysis

- Venoarterial ECMO applied to 7 patients
  - 6 under cardiopulmonary resuscitation

Rank-Preserving Structural-Failure Time Analysis Controlling for crossover in controls



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

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

to the control group. The second analysis used a rank-preserving structural-failure time model approach to attempt to recover the causal effect of ECMO. That approach yielded an estimated hazard ratio for death within 60 days of 0.51 (95% CI, 0.24 to 1.02). These three analyses all point to the same conclusion — ECMO probably has some benefit in this context, despite the trial not being traditionally positive. In addition, most of the other secondary outcomes favored ECMO.

Key Points

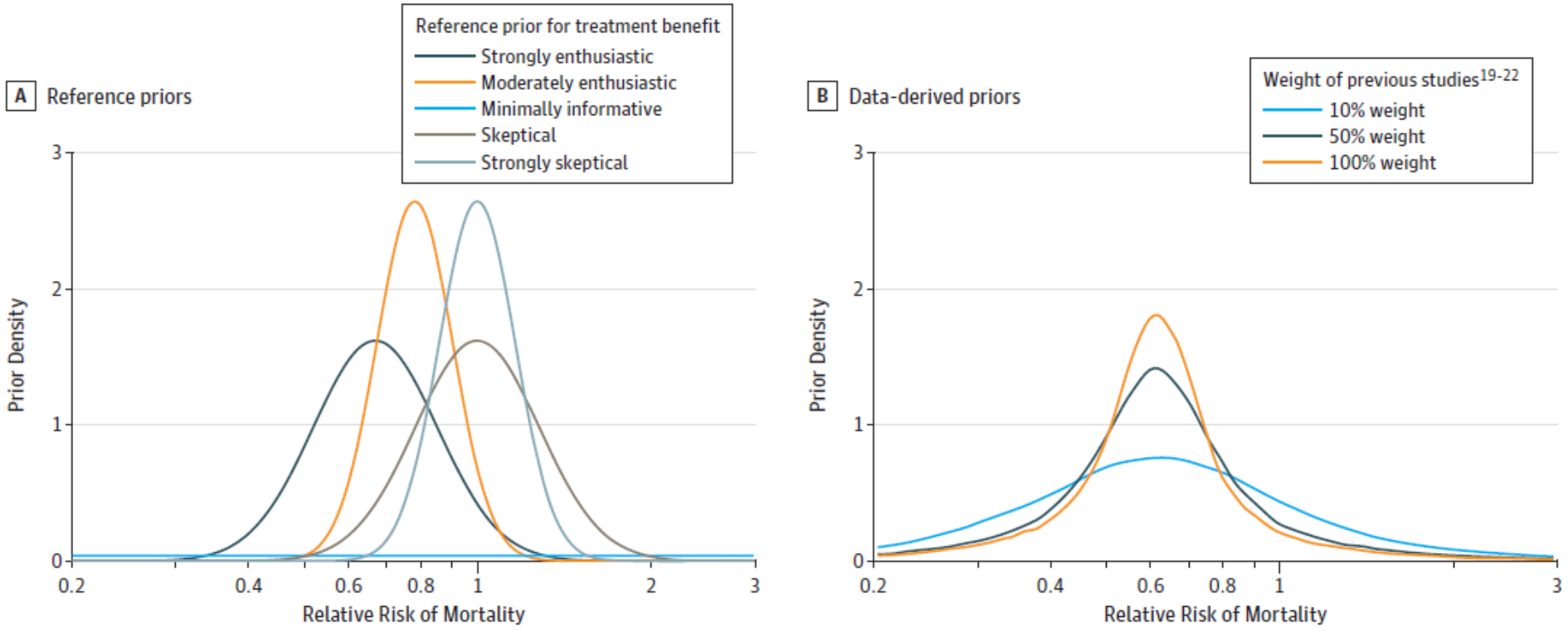
Question Can Bayesian analysis clarify the interpretation of clinical trial results?

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.

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. 2018;320(21):2251-2259.

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).

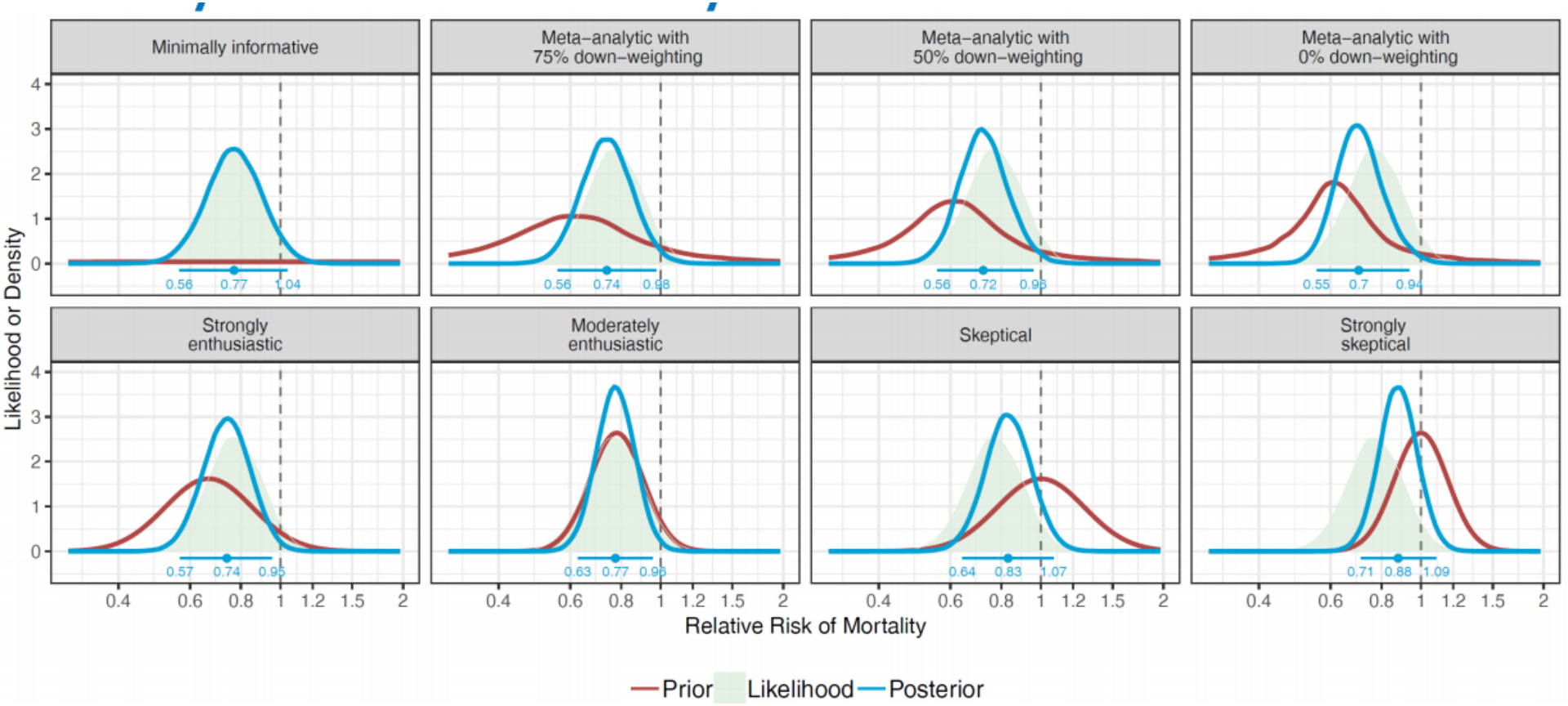

Minimally informative
Meta−analytic with 75% down−weighting
Meta−analytic with 50% down−weighting
Meta−analytic with 0% down−weighting
Strongly enthusiastic
Moderately enthusiastic
Skeptical
Strongly skeptical
Likelihood or Density
Relative Risk of Mortality
0.56 0.77 1.04
0.56 0.74 0.98
0.56 0.72 0.96
0.55 0.7 0.94
0.57 0.74 0.95
0.63 0.77 0.96
0.64 0.83 1.07
0.71 0.88 1.09
Prior
Likelihood
Posterior

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.

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.

Frequentist vs Bayesian inference

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

Roger J. Lewis, MD, PhD; Derek C. Angus, MD, MPH, FRCP

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 page 2251

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

JAMA. 2018 Dec 4;320(21):2208-2210.

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.

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 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]