Effect of Intraarrest Transport, Extracorporeal Cardiopulmonary Resuscitation, and Invasive Treatment

A Post Hoc Bayesian Reanalysis of a Randomized Clinical Trial

To the Editor:

Evidence for the effect of extracorporeal cardiopulmonary resuscitation (ECPR) from randomized controlled trials (RCTs) on survival with a favorable neurologic outcome is inconclusive.[1-3] The Prague Out-of-Hospital Cardial Arrest study was an RCT evaluating the use of an invasive strategy, including early intraarrest transport, ECPR, and immediate invasive management to standard resuscitation in refractory out-of-hospital cardiac arrest.[1] The study enrolled 256 patients with a median age of 58 years, 83% were men, and the median time of resuscitation was 52.5 min. The primary outcome of 180 days' survival with a favorable neurologic outcome (cerebral performance category 1 or 2) was reached in 31.5% of patients in the invasive strategy group and 22.0% of patients in the standard resuscitation strategy group (OR, 1.63; 95% CI, 0.93-2.85; absolute difference, 9.5%; 95% CI, −1.3% to 20.1%; $P = .09$).[1] This difference was not statistically significant using the frequentist approach, and the primary outcome result was interpreted as neutral.[1] An unreasonable, simplistic, yet common, practice is to label a trial as either positive or negative based on a difference in the primary outcome evaluated by a P value threshold of .05.[4] Bayesian analysis may provide a comprehensive view of the data, especially when the benefits of an intervention are uncertain.[5] Therefore, we performed a previously unplanned Bayesian reanalysis of the prespecified primary outcome while adhering to the intention to treat principle.

Overall, normal priors were specified for the log(OR), and seven scenarios were considered which determined the prior mean and SD. As a reference, a weakly informative prior was considered assuming no intervention effect (zero mean of log[OR]) and a large prior SD of 10. This weak prior was used to produce results that relied strongly on data from the RCT alone. Three (mildly, moderately, and strongly) enthusiastic priors were established with prior ORs of 1.70, 2.15, and 2.65 corresponding to 10%, 15%, and 20% improvement in the primary outcome in the invasive arm. The prior SD of log(OR) was equal to 0.2, 0.5, and 1.0. That is, with increasing prior value of the OR, a lower degree of prior belief was considered. These three priors were based on three scenarios published in the statistical analysis plan prior to the study enrollment in 2012.[6] These scenarios were established based on the consensus of three experts, each of whom conducted independent literature reviews and made estimates. Finally, we considered three (mildly, moderately, and strongly) skeptical priors which assumed no effect of the invasive strategy (zero prior mean of log [OR]). The degree of skepticism was expressed by varying the prior SD of the log(OR) of 1.0, 0.5, and 0.2. We chose a range of priors to represent a wide spectrum of beliefs regarding the treatment effect. We did not assume a negative effect of the invasive strategy because of the findings of published observational studies and clinical trials in this field, which have shown either positive or neutral results of the ECPR strategy compared with standard treatment.[1-3] The analysis was performed using the R version 4.0.4 software (R Core Team), using the packages runjags and JAGS.[7,8]

The main results for the primary outcome of 180 days' survival with minimal or no neurologic impairment are shown in Table 1. Distribution of the logarithm of the OR for different scenarios is shown in Figure 1. The weakly informative scenario corresponds to the results of a frequentist analysis with an OR of 1.65, an effect difference of 9.6%, and a posterior probability of the effect difference > 0 of 96.1% in favor of the invasive arm. In the three enthusiastic scenarios reflecting qualified estimates before the study initiation, the ORs were 1.68, 1.76, and 1.70, with effect differences of 9.9%, 10.8%, and 10.2%, and posterior probabilities of 99.9%, 98.9%, and 97.4%, in favor of the invasive arm. In the three skeptical scenarios, the ORs were 1.58, 1.45, and 1.18, with effect differences of 8.9%, 7.2%, and 3.2%, and posterior probabilities of 95.3%, 93.6%, and 84.5%, in favor of the invasive arm.

TABLE 1] Bayesian Analysis of the Primary Outcome of Survival With Minimal or No Neurologic Impairment at 180 d

Scenario	Prior OR	Prior SD of log(OR)	OR (95% CI)	Effect Difference, % (95% CI)	Posterior Probability of the Effect Difference > 0, %
Weakly informative	1.00	10.0	1.65 (0.83-2.71)	9.6 (−1.2 to 20.2)	96.1
Mildly enthusiastic	1.70	0.2	1.68 (1.18-2.25)	9.9 (3.8 to 16.2)	99.9
Moderately enthusiastic	2.15	0.5	1.76 (1.01-2.73)	10.8 (1.7 to 20.2)	98.9
Strongly enthusiastic	2.65	1.0	1.70 (0.89-2.76)	10.2 (−0.3 to 20.4)	97.4
Mildly skeptical	1.00	1.0	1.58 (0.84-2.58)	8.9 (−1.7 to 19.0)	95.3
Moderately skeptical	1.00	0.5	1.45 (0.83-2.24)	7.2 (−1.7 to 16.9)	93.6
Strongly skeptical	1.00	0.2	1.18 (0.83-1.58)	3.2 (−3.1 to 9.2)	84.5

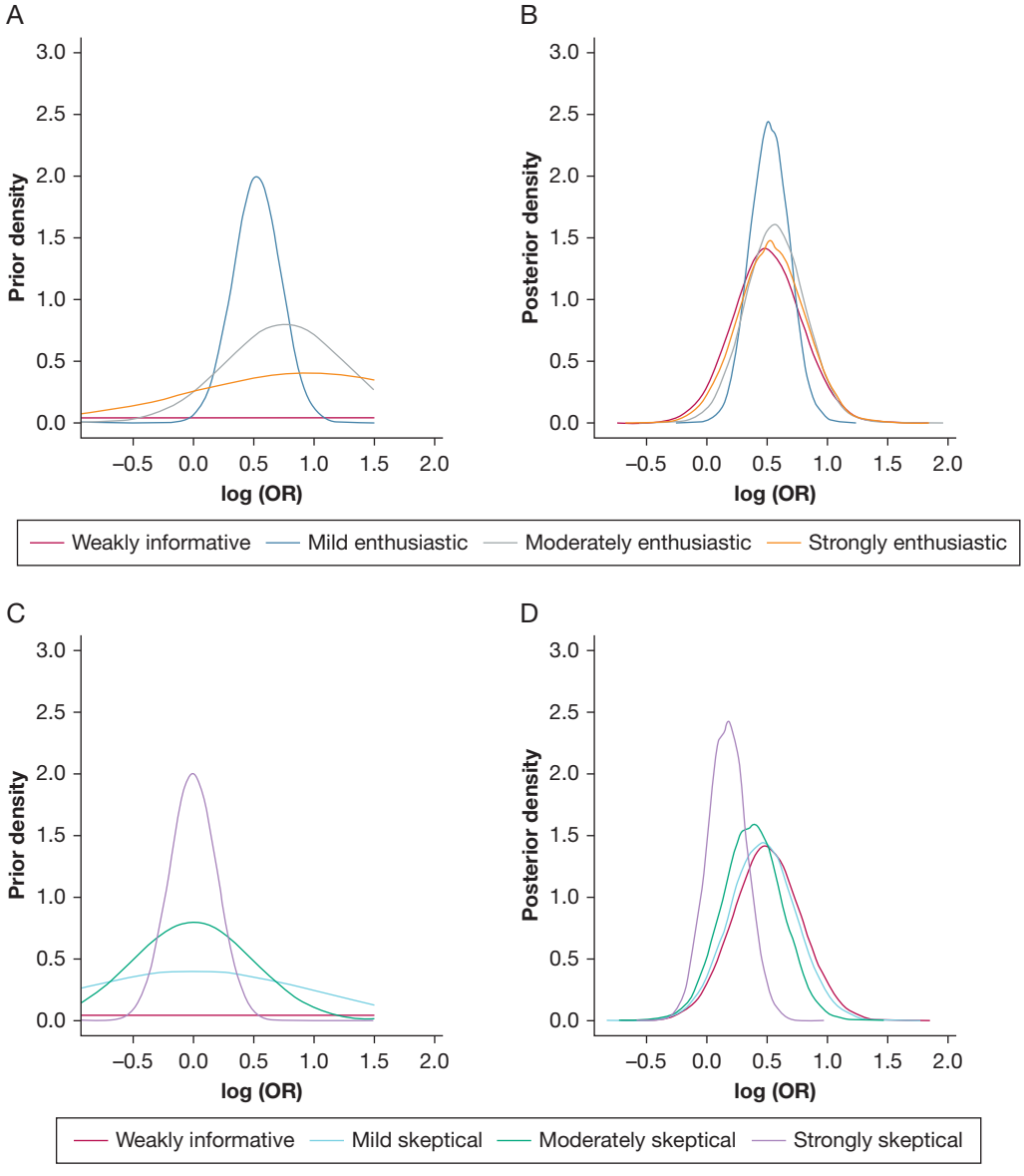

Figure 1 – *A and C, Prior and posterior (B and D) distribution for the logarithm of the OR for different scenarios.*

Limitations of this analysis include those of the primary trial.[1] Specifically, the study had a single-center design and was conducted in an experienced center, which limits the generalizability of our results. Additional limitations are specific to the Bayesian reanalysis. First, this is an unplanned post hoc analysis of the trial data. Furthermore, the accuracy of the results obtained from Bayesian analysis is always dependent on the prior distributions used. Recognizing this limitation, a wide range of potential prior beliefs was included in this analysis.

In conclusion, this Bayesian reanalysis of the study primary outcome showed a benefit of the invasive approach compared with standard resuscitation under a broad set of scenarios. This finding may help in the interpretation of the study results and underscores the importance of considering Bayesian analysis to complement frequentist approaches when evaluating the efficacy of interventions in clinical trials. Further research is warranted to gather additional evidence on the applicability, patient selection, and effectiveness of ECPR strategies across various centers and systems in improving outcomes for refractory out-of-hospital cardiac arrest.

Daniel Rob, MD, PhD
Arnošt Komárek, PhD
Jana Šmalcová, MD
Jan Bělohlávek, MD, PhD
Prague, Czech Republic

AFFILIATIONS: From the 2nd Department of Medicine – Department of Cardiovascular Medicine (D. R., J. Š., and J. B.), First Faculty of Medicine, Charles University in Prague and General University Hospital in Prague; and the Department of Probability and Mathematical Statistics (A. K.), Faculty of Mathematics and Physics, Charles University in Prague.

CORRESPONDENCE TO: Jan Bělohlávek, MD, PhD; email: jan.belohlavek@vfn.cz

DOI: https://doi.org/10.1016/j.chest.2023.07.030

Funding/Support

This study was supported by the General University Hospital in Prague [Grant MH CZ-DRO-VFN64165] and Charles University Research program "Cooperatio – Intensive Care Medicine".

Financial/Nonfinancial Disclosures

None declared.

Acknowledgments

Role of sponsor: The sponsor had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript.

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