A Bayesian Perspective
Extracorporeal CPR for Refractory Out-of-Hospital Cardiac Arrest

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Abstract

A recent randomized clinical trial, INCEPTION, reported in patients with refractory out-of-hospital cardiac arrest, extracorporeal CPR (eCPR) and conventional CPR (cCPR) had similar effects on survival with a favorable neurologic outcome. The current study examines if a Bayesian perspective provides additional quantative insights. Depending on the prior selected, the Bayesian approach for the INCEPTION intention-to treat (ITT) analysis shows an equivalence probability between 13.4 - 16.8% (defined as 1 / 1.1 < odds ratio (OR) < 1.1). The probability of clinical superiority with eCPR ranges from 65.7 - 77.0 % (defined as OR > 1.1). A similar analyses using INCEPTION per protocol (PP) data shows an equivalence probability between 4.7 - 20.2% with reduced probabilities of clinical superiority not exceeding 25%. It is concluded that a Bayesian perspective allows considerable additional quantative insights into the trial analysis and interpretation. The non-negligible probabilities of increased survival, or even harm, with their considerable residual uncertainties, suggests that additional studies are required before concluding that eCPR and cCPR have similar average survival effects.

Keywords: extracorporeal CPR, Bayesian statistics

1. Introduction

Out-of-hospital cardiac arrest is a frequent event and fortunately its devastating consequences can be partially mitigated by rapid commencement of basic life support with high-quality chest compressions and external defibrillation (conventional cardiopulmonary resuscitation (cCPR)). However, there remains a substantial subset of individuals who do not respond rapidly to these measures and whether more invasive measures. Whether the addition of more aggressive measure including extracorporeal CPR (the addition of extracorporeal membrane oxygenation to standard advanced cardiac life support (eCPR)) can improve survival and diminish anoxic brain injury is a current topic of research. A large randomized clinical trial (RCT) examining this question recently published their results[1]. For their primary outcome, 30 day survival without significant neurological deficit, an odds ratio of 1.4 (95% confidence interval, 0.5 to 3.5; P = 0.52) in favor of extracorporeal CPR was observed leading to the conclusion "In patients with refractory out-of-hospital cardiac arrest, extracorporeal CPR and conventional CPR had similar effects on survival with a favorable neurological outcome".[1]

This communication does not reiterate the many reasons to be wary of null hypothesis significance testing (NHST), p values and confidence intervals[2]. Rather it assumes the reader has perhaps heard that Bayesian

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methods mirror our intuitive learning and diagnostic processes and is curious about its potential application to RCT analyses and interpretations.

Therefore the goal of this communication is to examine whether a Bayesian perspective permits additional insights into the specific clinical question regarding any added value of eCPR following an out-of-hospital arrest in patients refractory to cCPR.

2. Methods

The data for the primary outcome, 30 day survival with intact neurological status, based on an intention to treat (ITT) analysis was abstracted from the original INCEPTION trial[1] and used for the primary analysis. The ITT analysis has the advantage of minimizing bias by preserving the prognostic balance afforded by randomization as well as assuring the validity of the accompanying statistical analyses.

Bayesian analytical approaches provide a number of benefits over the classical NHST approach, including parameter estimation accompanied by direct probability statements about parameters of interest (herein the risk of survival with intact neurological status), and the incorporation prior knowledge[3,4].

These probability statements arise from the posterior distribution according to the Bayes Thereom, expressed as follows:

$$\text{Posterior} = \frac{\text{Probability of the data} * \text{Prior}}{\text{Normalizing Constant}}$$

Therefore, in addition to the current data summarized by the probability of the data (likelihood function), prior probability distributions are required. Because our main focus is the analysis and interpretation of the INCEPTION trial[1] alone, our primary analysis used a default vague parameter prior ($log(\theta) \sim Normal[0, 2.50]$, thereby assuring that the posterior distribution is dominated by the observed INCEPTION[1] data.

The robustness of the Bayesian approach is often assessed by sensitivity analyses that examine the variation in the posterior probability as a function of the choice of different prior distributions. Incorporating prior information underscores another important advantage of Bayesian analyses, the ability to learn sequentially. There were two previous RCTs examining extracorporeal CPR[5,6] and while the protocols are not identical, it may be reasonable to allow this data to serve as informed priors for the eCPR parameter, which can be updated with the INCEPTION[1] data.

Therefore, in addition to the vague prior described above, we considered three possible informative priors
i) a **combined** prior using all the available prior RCT data[6,5]
ii) an **enthusiastic** prior, so labelled since this uses only the ARREST data, a trial stopped prematurely for efficacy
iii) a **skeptical** prior, so labelled since this uses only the PRAGUE data, a trial stopped prematurely for futility

This prior information of the probability of eCPR success in each previous trial, X_i, can be summarized as a normal distribution with a mean equal to the proportion of successes, $\hat{p}_i$ with a standard deviation equal to

$$\sqrt{\hat{p}_i * (1 - \hat{p}_i)}$$

As baseline success rates for cCPR varies markedly between the three studies, it was decided to maintain the INCEPTION control baseline with the vague prior for all analyses and to update only the eCPR arm with prior information.

Posterior distributions are summarized with medians and 95% highest-density intervals (credible intervals (CrI)), defined as the narrowest interval containing 95% of the probability density function[7]. Bayesian analyses permit not only calculations of the posterior probability of any additional survival with eCPR (OR >1.00), but also of clinically meaningful benefits. While there is no universal definition for a clinically

meaningful benefit, a survival OR >1.10 may be an acceptable threshold for many. Bayesian analyses also allows calculation of the probability between any two points. For example, rather than simply comparing if the survival of one treatment is better than another, one can calculate a range of practical equivalence (ROPE) between treatments. While different ranges may be proposed, +/- 10% seems a reasonable small difference that many woul consider as equivalent.

ITT assesses subjects based on the group they were initially (and randomly) allocated to, regardless of whether or not they dropped out, were fully adhered to the treatment or switched to an alternative treatment. In superiority trials, ITT analyses can therefore be seen as a conservative estimate which mirrors clinical effectiveness. In contrast, a per protocol (PP) analysis accounts for adherence by analyzing only those patients who completed the treatment they were originally allocated to. While PP may provide additional insights into efficacy, it is subject to bias. Since a PP analysis when performed in conjunction with an ITT analysis may provide additional insights, this has also been subjected to a Bayesian analysis.

Posterior distributions were estimated using the Hamiltonian Monte Carlo,a form of Markov Chain Monte Carlo simulations in which the gradient of the log posterior is used to efficiently sample the posterior space. This was implemented in `Stan`[8] using the front end `rstanarm` package[9] by fitting a logistic regression model with a single treatment parameter. All analyses were executed using `R`[10] within the integrated development environmentof RStudio[11]. Model convergence was assessed by examination of the Monte Carlo Standard Error $< 10\%$ of the posterior standard deviation, n_{eff} an estimate of the effective number of independent draws from the posterior distribution of the estimand $> 10\%$ maximum and $\hat{R}$ a measures the ratio of the average variance of samples within each chain to the variance of the pooled samples across chains < 1.1. Reporting has followed the Bayesian Analysis Reporting Guidelines[12]. The statistical code can be found on Github (https://github.com/brophyj/eCPR).

3. Results

ITT data from the INCEPTION trial[1] and two other pertinent trials[5,6] that also randomized out of hospital cardiac arrest patients to cCPR to eCPR are shown in Table 1. Performing a Bayesian analysis on the INCEPTION[1] trial, using a default vague prior, produces an odds ratio (OR) 1.32 with 95% CrI 0.54 - 3.22. The closeness of this result to the original analysis (OR, 1.4; 95% CI 0.5 - 3.5) confirms the minimal impact of the default vague prior and reveals a Bayesian analysis completely dominated by the observed INCEPTION[1] data.

One of the advantages of a Bayesian approach is the ability to make direct probability statements about the estimand of improved eCPR survival. The eCPR probability density function for improved survival from INCEPTION[1] data with the default vague prior is displayed in Figure 1 and reveals that the probability of enhanced survival with eCPR is 72.7%. The probability that the improved survival exceeds a 10% improvement is 65.7% and the ROPE probability is 13.4% (Table 2).

Three different informative priors were considered i) a N(0.32, 0.47) ii) a N(0.43, 0.49) iii) a N(0.31, 0.46) distributions to represent all the combined available RCT data[5,6], only the ARREST[6] data and only the PRAGUE[5] data, respectively. These different prior probabilities were updated using with the INCEPTION[1] ITT data to create the posterior distributions displayed in Table 2. The posteriorprobability for enhanced eCPR survival has increased to 80.4% with a skeptical prior, to 84.9% with the enthusiastic prior and, as expected, the associated uncertainty has been reduced, as reflected by the narrower 95% CrI, with the additional data.

The probability that the eCPR survival improvements exceed a minimum 10% clinical threshold for improvement are 71% and 77% for the skeptical and enthusiastic priors, respectively. The corresponding ROPE probabilities are 16.8% and 13.8% (Table 2). Posterior probabilities with the combined prior were as expected between the results with the skeptical and enthusiastic priors. The graphical presentations of these results are shown in Figure 2.

INCEPTION[1] did not report a per-protocol analysis. Such an analysis may be helpful in assessing treatment efficacy, unfortunately at the risk of an increased risk of bias by not respecting the ITT principle. From INCEPTION[1] Figure S4[1], it appears that the per protocol data for mortality is 13 survivors from 61 patients in the cCPR group compared to 5 survivors from 46 patients receiving eCPR. With a vague prior, the OR of increased survival with eCPR compared to cCPR is decreased but with very wide CrI (OR 0.45, 95% CrI 0.15 - 1.35), limiting any definitive conclusions. The decreased eCPR success rates in the INCEPTION[1] per protocol data results in reduced posterior probabilities of eCPR benefit and an increased probability of equivalence or benefit with cCPR. The probabilities of eCPR survival compared to cCPR using the per protocol data and incorporating the previously identified informative priors are shown in Table 3.

4. Discussion

This Bayesian analysis of the INCEPTION[1] ITT data alone (analysis with a vague prior) suggests the presence of a non-negligible mortality probability benefit with eCPR, in the range of 73%, compared to cCPR. The probability that this improvement in survival exceeds 10% is almost 66%. The consideration of pertinent prior information from two previous comparable RCTs[6,5] results in estimates of improved eCPR survival probabilities, with intact neurological status, in the vicinity of 80-85%. Moreover depending on the choice of prior beliefs included, the posterior probability of at least a 10% improved eCPR survival is in the range of 71 - 77% probability. In contrast to the INCEPTION[1] original conclusion of similar survival effects between the two treatments, this re-analysis suggests only a modest probability of approximately 15% that survival probabilities between the two techniques are within a reasonably acceptable equivalency range. Additional uncertainty about the benefits or harms of eCPR do arise with the per protocol analysis, both with and without informative priors.

The INCEPTION[1] researchers have addressed an important clinical question in the most challenging of research environments and are to be congratulated on their trial design, its execution, and a nuanced discussion. However the natural constraints of standard statistical analyses, also known as null hypothesis significance testing, limits the quantitative appreciation of their data, and prevents a full and comprehensive exploitation and updating of past knowledge. For trials such as INCEPTION[1] that fail to meet statistical significance and are often incorrectly thought of as "negative" trials, null hypothesis significance testing favors confusion "between absence of evidence and evidence of absence"[13]. Rather than dichotomizing results into statistical significance or not, with an obligatory loss of information and understanding, Bayesian analysis concentrates on estimation of key outcome differences with direct probability measures of their uncertainty.

Although this Bayesian analysis presents the strengths noted above, it also had limitations. First, we did not have access to individual data from any of the trials limiting the possibility of examining specific subgroups. Also for the per protocol analysis, this data was only available for survival and not the primary INCEPTION[1] outcome that included survival with intact neurological status. The threshold choices for superiority and equivalence may be seen as arbitrary, although the analyses can be easily repeated for different choices. Given the existence of only 3 trials estimating the very divergent baseline cCPR rates could not be reliably modeled. We choose not to perform a traditional Bayesian meta-analysis with a semi-informative prior for the between-study variation because our goal was to illustrate how Bayesian principles could be informative when applied to the analysis and interpretation of new trial data, in situations both with and without previous knowledge.

The "take home" message from this study is that standard statistical analyses resulting in a conclusion of "similar survival effects of eCPR to cCPR" may be overly simplified and potentially inaccurate. This Bayesian analysis demonstrates that at present definitive conclusions regarding the superiority, inferiority, or equivalence are impossible. Rather the possibility of a clinically meaningful benefit, or less likely the possibility of clinically meaningful harm, has not been reasonably excluded and continued research is necessary to clarifying the residual uncertainties. The final dilemma confronting clinicians is that even Bayesian

analyses of randomized trials provide only probability estimates for *average* treatment effects and not for the elusive *individual* treatment effect.

5. Tables

Table 1 Extracted ITT trial data

Trial	Fail CPR (n)	Fail eCPR (n)	Success CPR (n)	Success eCPR (n)
INCEPTION	52	56	10	14
ARREST	14	8	1	6
PRAGUE	108	86	24	38

eCPR = extracorporeal cardiopulmonary resuscitation

Table 2 eCPR odds ratios, 95% credible intervals and probabilities with various priors

Priors	OR	95% CrI		Probabilities		
	point estimate	lower limit	upper limit	p(OR) >1	p(OR) >1.1	p(ROPE)
Vague	1.321	0.543	3.215	0.727	0.657	0.134
Combined	1.349	0.705	2.580	0.817	0.732	0.153
Enthusiastic	1.403	0.738	2.668	0.849	0.770	0.138
Skeptical	1.322	0.700	2.496	0.804	0.710	0.168

Vague: default vague prior
Combined: prior eCPR data from ARREST + PRAGUE
Enthusiastic: prior eCPR data from ARREST alone
Skeptical: prior eCPR data from PRAGUE alone
ROPE: range of practical equivalence = + / - 10% OR (odds ratio)

Table 3 eCPR (per protocol) odds ratios, 95% credible intervals and probabilities with various priors

Priors	OR	95% CrI		Probabilities		
	point estimate	lower limit	upper limit	p(OR) >1	p(OR) >1.1	p(ROPE)
Vague	0.451	0.151	1.348	0.070	0.049	0.047
Combined	0.859	0.430	1.713	0.330	0.238	0.202
Enthusiastic	0.870	0.437	1.734	0.345	0.251	0.201
Skeptical	0.858	0.419	1.755	0.327	0.237	0.197

Vague: default vague prior
Combined: prior eCPR data from ARREST + PRAGUE
Enthusiastic: prior eCPR data from ARREST alone
Skeptical: prior eCPR data from PRAGUE alone
ROPE: range of practical equivalence = + / - 10% OR (odds ratio)

6. Figures

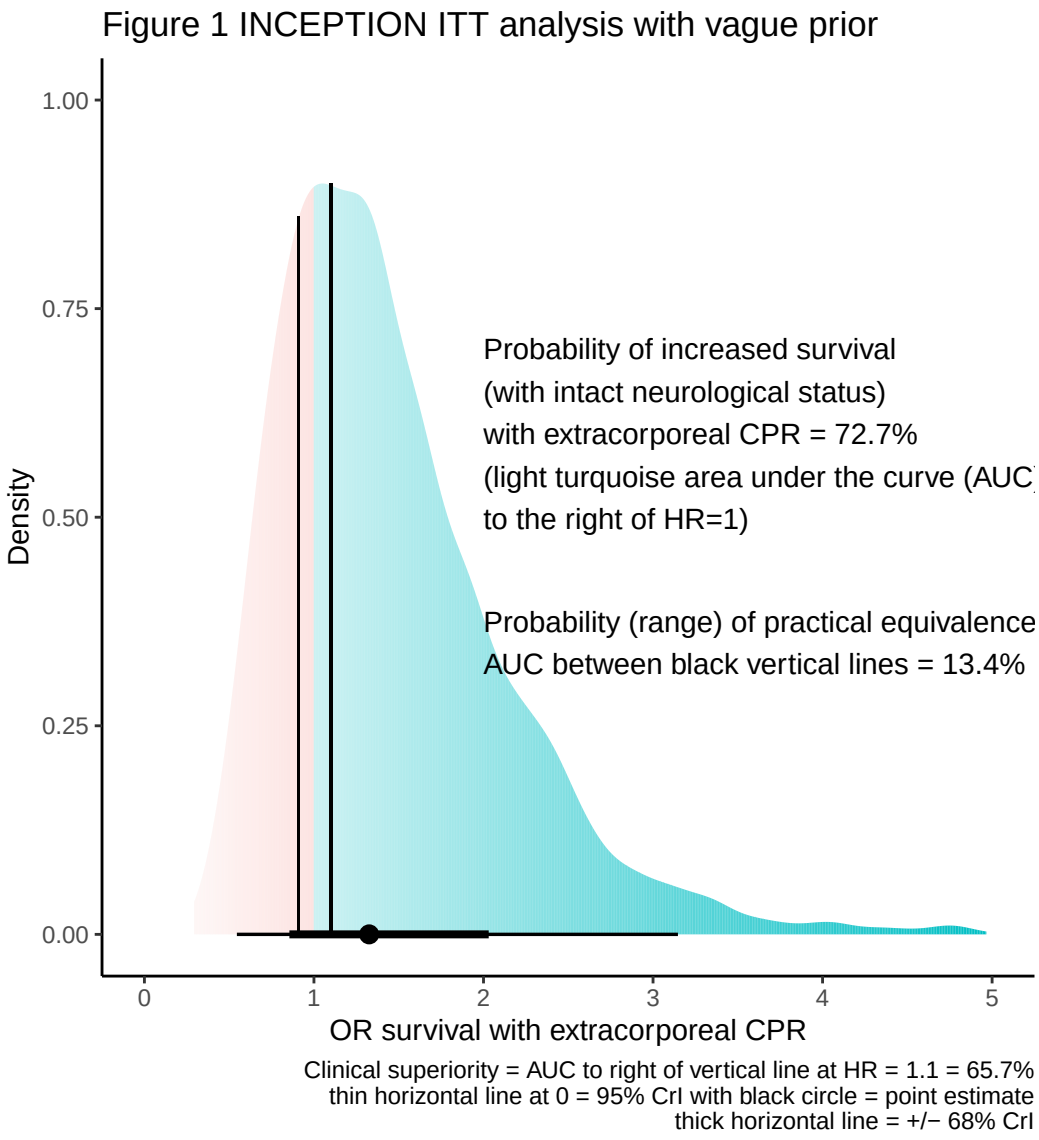


Figure 1 INCEPTION ITT analysis with vague prior
1.00
0.75
0.50
0.25
0.00
Density
0
1
2
3
4
5
OR survival with extracorporeal CPR
Probability of increased survival
(with intact neurological status)
with extracorporeal CPR = 72.7%
(light turquoise area under the curve (AUC
to the right of HR=1)
Probability (range) of practical equivalence
AUC between black vertical lines = 13.4%
Clinical superiority = AUC to right of vertical line at HR = 1.1 = 65.7%
thin horizontal line at 0 = 95% CrI with black circle = point estimate
thick horizontal line = +/− 68% CrI

Figure 2. Probability density plots with informative priors

Figure 2a INCEPTION ITT analysis with combined prior*

*data from ARREST and PRAGUE

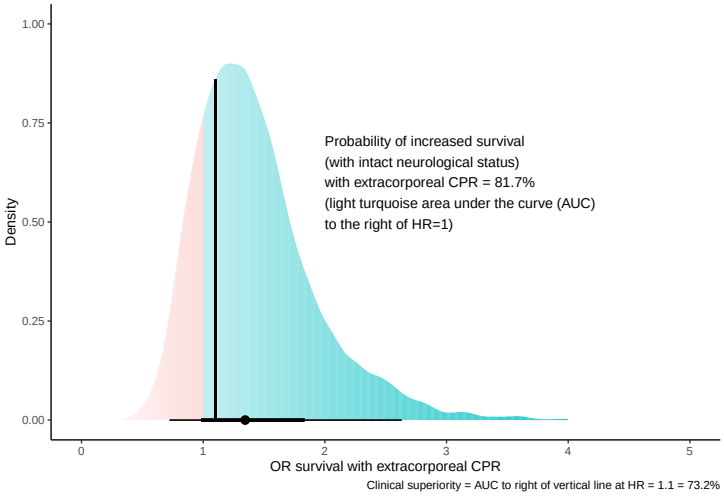


Figure 2b INCEPTION ITT analysis with enthusiastic prior*

*data from ARREST alone

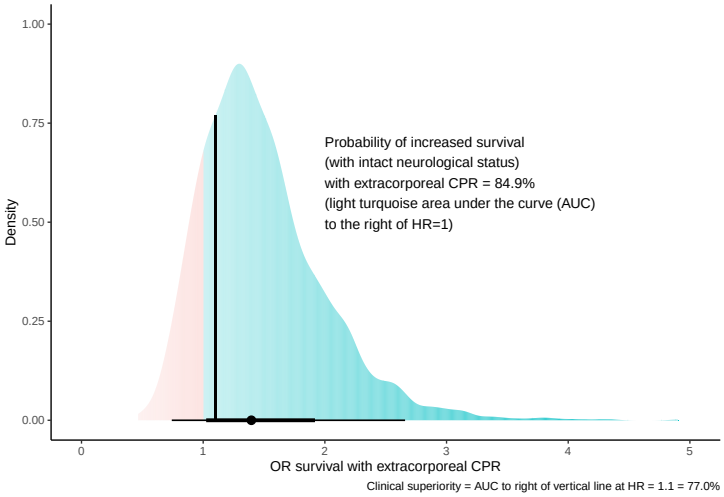
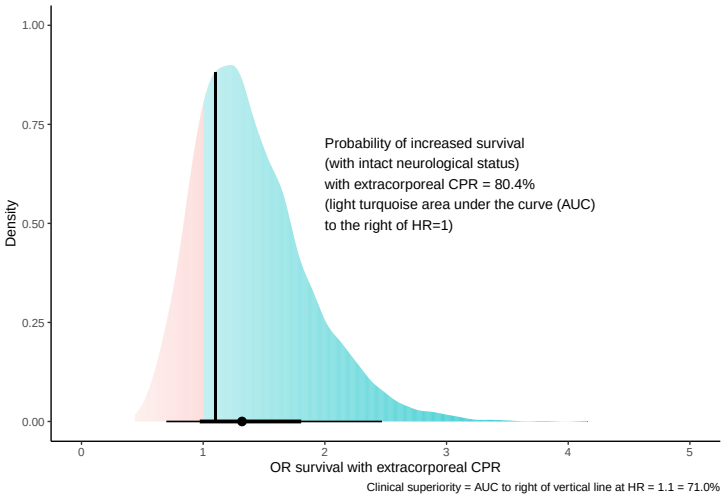


Figure 2c INCEPTION ITT analysis with skeptical prior*

*data from PRAGUE alone



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