

Pacemaker risk following transcatheter aortic valve replacement - A Bayesian reanalysis

Arthur M. Albuquerque^{a,1}, James M. Brophy^{b,*,2}

^a School of Medicine, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil

^b McGill Health University Center, Montreal, Canada

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ABSTRACT

Objectives: To estimate the probability of increased total mortality risk in patients receiving a cardiac pacemaker following transcatheter aortic valve replacement (TAVR).

Background: A recent publication of a nationwide Swedish, population-based cohort study found no statistically significant difference for all-cause mortality. It is unknown if a Bayesian reanalysis would provide additional insights and lead to the same conclusion.

Methods: A digitalized approach to the published Kaplan – Meier curves was used to reconstruct the individual patient dataset. Bayesian survival analyses of this data using both vague, thereby allowing the posterior probability to be completely dominated by the observed data, as well as skeptical and informative priors, based on the mortality risk of pacemaker implantation following surgical aortic valve replacement, were performed.

Results: The individual patient data set was reliably reconstructed and showed a 4 year follow-up hazard ratio (HR) = 1.08, 95% credible interval (CrI) 0.85–1.36. The Bayesian analysis using a vague prior revealed a 74.9% probability of increased mortality in the pacemaker group. Using a skeptical, semi-informative, and fully informative priors, the posterior probabilities of increased mortality following pacemaker insertion was increased to 68.9%, 93.9% and 98.4%, respectively.

Conclusions: This Bayesian reanalysis suggests a moderate to high probability of an increased total mortality in TAVR patients requiring post procedural pacemaker implantation.

1. Introduction

Recently, a nationwide Swedish, population-based cohort study found no statistically significant difference for all-cause mortality (hazard ratio [HR] 1.03; 95% CI: 0.88–1.22; $P = 0.692$) in patients who underwent permanent pacemaker implantation after transcatheter aortic valve replacement (TAVR) between 2008 and 2018 [1]. While the study included a large unselected sample of 3420 TAVR patients, there are a number of reasons why it is of interest to query the strength of the evidence supporting the conclusion that long-term survival between patients who did and did not undergo permanent pacemaker implantation after TAVR is not different.

First, their central Kaplan–Meier curve shows survival curves crossing, raising the possibility of a time-varying HR such that the

proportional hazards assumptions underlying their analysis may not be valid. Second given this is an elderly population (mean age > 81), the performed comparative lifetime analysis with some patients followed up to 10 years may not be the most informative and clinically relevant. As eventually we all die, this analysis perhaps obscures some earlier clinically pertinent mortality differences among those receiving and not receiving pacemakers peri-TAVR. Thirdly, the same nationwide data-bases have examined the mortality impact of pacemaker implantation in a contemporary population of aortic stenosis patients undergoing surgical aortic valve replacement (SAVR) [2] and the inclusion of all or some of this additional evidence may be informative.

A Bayesian analysis [3] can directly estimate the probability of increased mortality post pacemaker insertion and allows the incorporation of past knowledge which may be helpful in furthering our

* Corresponding author at: Medicine & Epidemiology (McGill University), McGill University Health Center, 1001 Decarie Blvd Room C04.1410, Montreal, Qc H4A 3J1, Canada.

E-mail address: james.brophy@mcgill.ca (J.M. Brophy).

¹ This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

² This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

understanding of this data and in presenting actionable probabilities.

2. Methods

2.1. Data source

To gain approximate access to this dataset, we digitalized the reported Kaplan–Meier mortality curve in the propensity score-matched cohort [1]. We extracted this data instead of from the full cohort since propensity score matching yields more balanced comparative groups than provided by the crude data. This was operationalized by following the technique of Guyot [4], utilizing the website WebPlotDigitalizer and the R programming language [5]. Specifically, the R package IPD-fromKM [6] created this reconstruction of the individual patient data thereby allowing our secondary Bayesian survival analyses to be performed.

2.2. Outcome

While the original publication examined several different outcomes, this analysis is limited to the main outcome of total mortality as that is the only outcome for which we can estimate Kaplan–Meier-derived individual patient data (IPD). Given that the median follow-up is 2.7 years, that the KM slopes appear to change beyond 4 years and that assessing the impact of pacemaker implantation seems clinically most relevant in this shorter time window, we prespecified a maximum 4 year follow-up for our analyses.

2.3. Statistical analyses

Bayesian approaches to survival analysis can provide a number of benefits over the classical frequentist approach, including the ability to make direct probability statements about parameters of interest (the risk of pacemaker implantation), and to incorporate prior knowledge [7,8]. These probability statements arise from the posterior distribution according to the following equation:

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

Therefore, in addition to the current data summarized by the probability of the data (likelihood function) one requires a prior probability distribution each parameter. 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.

The mechanics of the Bayesian analyses were performed using the Stan programming language [9] through the R package rstanarm [10]. We fitted a proportional hazard regression model using cubic M-splines for the baseline hazard. Bayesian analyses require a prior distribution for each parameter. In this model, parameters were the intercept, M-spline coefficients, and the pacemaker exposure log hazard ratio. Because our focus in this article was on the latter, we used rstanarm's default vague priors for the intercept and M-spline coefficients (Normal[0,20] and Dirichlet[1, 1, 1, ...], respectively) in all analyses.

To assess robustness of results, we estimated pacemaker exposure log hazard ratio's marginal posterior distribution with four different priors. First we performed the analysis using rstanarm's built-in default vague prior (Normal [0, 2.50]; mean and standard deviation prior). This prior contributes very little information to the posterior distribution and allows it to be completely dominated by the data. Second, we used a skeptical prior, defined as a low prior belief that peri-procedural pacemaker implantation is associated with increased mortality. This prior was based on data from the Placement of Aortic Transcatheter Valve Among (PARTNER) 2 studies of 3763 intermediate or high surgical risk patients undergoing TAVR [11]. The reported 1-year mortality adjusted hazard ratio for pacemaker exposure (HR 0.99; 95% CI 0.65 to 1.49) was

transformed to a Normal [−0.01, 0.21] skeptical prior. Third, we used a semi-informative prior based on a previous study, using the same nationwide Swedish databases as the article reanalyzed here [2], but in a cohort of almost 25,000 patients undergoing SAVR [2]. We down-weighted the influence of this informative prior by 50%, because while the populations are similar (everyone has aortic stenosis) and studied in the same institutions, the aortic valve interventions were different and the long-term evolution of SAVR patients receiving pacemakers may not be identical to TAVR patients. To downweight, we increased the original standard error by 50% (hereafter labelled “SAVR 50%”). This study reported an increased mortality risk with pacemaker implantation (HR 1.14; 95%CI, 1.01–1.29) which was transformed to a Normal[0.13, 0.094] semi-informative prior. Lastly, we created a fully informed prior based on the same data, but with 100% of weight (Normal[0.13, 0.062]; hereafter labelled “SAVR 100%”).

Marginal posterior distributions are summarized with medians and 95% highest-density intervals (credible intervals), defined as the narrowest interval containing 95% of the probability density function [12]. We not only calculated the posterior probability of any harm (HR >1.00), but also of greater harms (HR >1.10 and HR >1.25). In addition, we converted hazard ratio marginal posterior distributions to the absolute scale (risk difference [RD]) and estimated different posterior probabilities (RD >0%, RD >1%, and RD >2%). We assumed a baseline mortality risk (no pacemaker group) of 39.9% at 4 years [13], based on the digitalized extracted data mentioned above [1].

All analyses were executed within the integrated development environment of RStudio and the statistical code can be found on Github (https://github.com/brophyj/tavr_pace).

3. Results

3.1. Verifying individual data extraction

Quality assessment of our Kaplan–Meier-derived IPD data extraction was performed analytically by comparing our extracted overall hazard ratio and 95% CI with the published values, and graphically by checking the derived Kaplan–Meier (KM) curves (Fig. 1) with the published propensity-matched KM curve (Original Supplemental Fig. 2 [1]). Not only is the data extraction judged to be adequate graphically but also numerically with a calculated HR = 1.02, 95% CI 0.84–1.24 which compares favorably with the published value (HR: 0.99; 95% CI: 0.81–1.21).

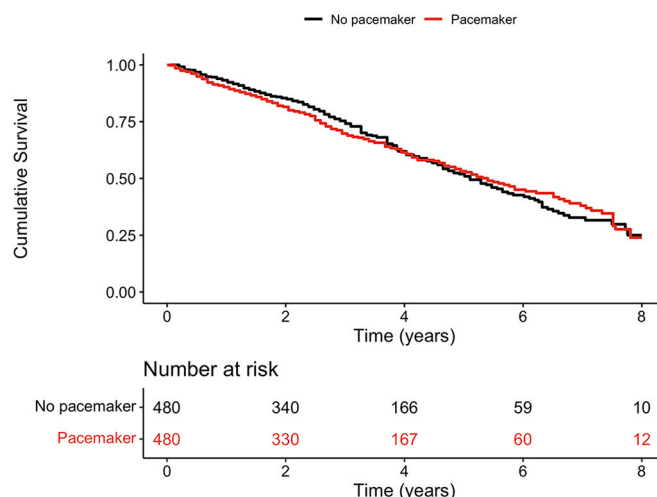


Fig. 1. Reconstructed Kaplan–Meier curve.

This figure shows the reconstructed Kaplan–Meier all-cause mortality curve regarding the individual-patient data extracted from the propensity score-matched cohort.

The difference in survival probabilities with the 95% CI is plotted in Fig. 2. One of the concerns with the original analysis was the possibility of time-varying proportional hazards which are again suggested in this Figure. However, statistical tests suggested the proportional hazards assumption was not violated ($p = 0.11$), although it bears mentioning that the power to detect violations with this sample size is limited [14].

3.2. Standard survival analysis to 4 years

Even if the proportional hazards assumptions are not violated, clinically it is indicated to investigate the risks over a more restricted time window. In accordance also with the varying risks, we elected a priori to concentrate on a 4-year time window. Using this time frame, we extracted the individual data as described in the Methods section above. The frequentist Cox proportional hazards model analysis for this more restricted data set results in a HR = 1.14, 95% CI 0.90–1.43, $p = 0.27$. The 4 year point estimate has moved towards an increased mortality risk in the pacemaker group, but the result remains not statistically significant. However, using this statistically non-significant result to conclude that a pacemaker does not influence 4-year mortality risks makes the common error of confusing absence of evidence with evidence of absence. To avoid the nullism and dichotomania associated with null hypothesis significance testing [15], we next explored the data with a Bayesian survival analysis.

3.3. Bayesian survival analysis

Using a vague prior, the Bayesian HR at a 4 year time point is 1.08, 95% credible interval (95% CrI 0.85–1.36). While the CrI approximates the previously calculated CI, it can now be used to formulate direct probability statements. As shown in Fig. 3 and Table 1, the use of a pacemaker is compatible with an 74.9% probability, calculated as the area under the curve to the right of HR = 1.0, of increased mortality compared to those not receiving a pacemaker.

While the incorporation of a vague prior allows one to calculate

posterior probabilities, it does not introduce relevant external information into the analysis, limiting the extent to which the Bayesian framework can contribute. Further analyses with more informative priors could cover different beliefs on this subject. When assuming a skeptical prior based on a large observational study [11], there is an increased power, represented by the narrower credible interval (95% CrI 0.86–1.27), and slightly smaller probability of increased mortality (Fig. 3 and Table 1).

Other scientifically justified beliefs can be incorporated and the robustness of the final (posterior) probabilities assessed. For example, informative priors based on the risk of pacemaker implantation in aortic stenosis patients from the same Swedish databases, but undergoing SAVR [2] could be used. The choice for this informative prior is justified by the similarities in the populations with treatments taking place in the same hospital centers at contemporary time windows. This informative prior may be downweighted, if so desired to account for the additional uncertainty associated with the varying type of aortic valve intervention. As shown in Fig. 3 and Table 1, these informative priors lead to high posterior probabilities, from 93.9% to 98.4%, of increased 4 year mortality following TAVR pacemaker insertion.

Another advantage of Bayesian analyses is the ability to calculate posterior probabilities other than of any harm (HR > 1). As shown in Table 1, while it is somewhat unlikely that the relative risk associated with a pacemaker exceeds a 25% increase, there is a moderate probability (34–67%) that the relative risk exceeds a 10% increase.

Lastly, to aid clinical decision-making, we estimated the marginal posterior distributions on risk differences (RDs). These distributions varied according to the underlying belief (Table 1). The posterior probabilities of any harm on both relative (HR > 1.00, Table 1) and absolute scale (RD > 0%, Table 1) are, as expected, identical. Moreover, we estimated the posterior probabilities of absolute mortality increase association with pacemaker exposure by 1% and 2%. The posterior probability of RD > 1% varied between 58.0% to 94%.

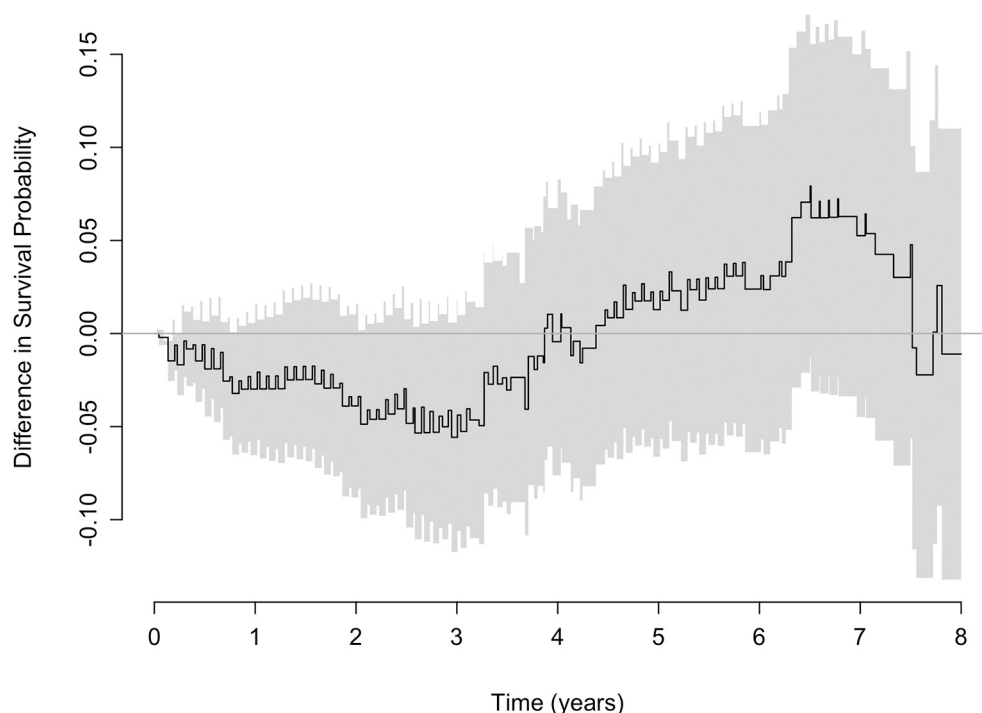


Fig. 2. Difference in Survival Probability Across Time.

This figure shows the difference in survival probabilities along with 95% confidence intervals (gray area) across time in years. A difference smaller than zero indicates lower survival probability in patients exposed to pacemaker.

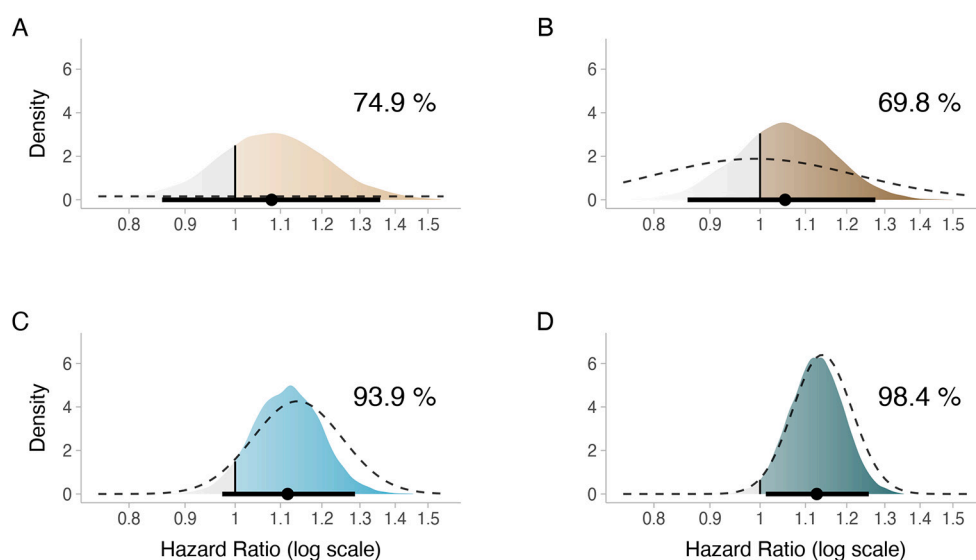


Fig. 3. Marginal Prior and Posterior Distributions of the Hazard Ratio (4-year time window).

Underlying marginal prior and posterior distributions regarding analyses restricted to 4-year time-window (Table 1). Panel A, Vague prior; B, Skeptical prior; C, Semi-informative prior “SAVR 50%”; D, Fully informative prior “SAVR 100%.” Dashed lines depict the underlying marginal prior distributions. Color filled distributions represent the marginal posteriors. Interval bars depict the median and 95% credible intervals of each marginal posterior distribution. Colored filled areas depict the area under the curve above HR of 1.0, which represents the posterior probability above 1.0. These probabilities are also shown in each panel. In a similar manner, the probability of exceeding a HR of 1.1 or 1.25 can be found by calculating the area under the curve to the right of the vertical line at HR = 1.1 and HR = 1.25, respectively (Table 1).

Table 1.
Posterior survival probabilities as a function of varying prior information

Belief	HR (95% CrI)	Posterior probability, %		
		HR > 1.00	HR > 1.10	HR > 1.25
Vague	1.08 (0.84, 1.34)	74.9	43.6	10.3
Skeptical	1.05 (0.86, 1.27)	69.8	33.9	4.4
Semi-informative SAVR 50%	1.12 (0.96, 1.27)	93.9	57.9	5.6
Fully-informative SAVR 100%	1.13 (1.01, 1.26)	98.4	66.7	3.1
Belief	RD (95% CrI)	RD > 0%	RD > 1%	RD > 2%
Vague	2.4 (−4.8, 9.8)	74.9	64.7	54.2
Skeptical	1.6 (−4.5, 7.8)	69.8	58.0	45.2
Semi-informative SAVR 50%	3.5 (−1.2, 7.7)	93.9	86.2	73.2
Fully-informative SAVR 100%	3.8 (0.4, 7.4)	98.4	94.0	83.3

The assumed fixed baseline risk was 39.9%, based on the SWEDEHEART TAVR data on patients not exposed to pacemaker at 4 years.

“Semi-informative SAVR 50%” regards posterior distribution while assuming a prior based on the surgical aortic valve replacement SWEDEHEART data with 50% of weight. “Fully-informative SAVR 100%” regards the same data, but with 100% weight.

Abbreviations: HR, hazard ratio; RD, risk difference; CrI, credible interval.

4. Discussion

Bayesian approaches to survival analysis can provide a number of benefits over the classical frequentist approach, including the ability to make direct probability statements about parameters of interest (the risk of pacemaker implantation), and to incorporate prior knowledge. In this Bayesian reanalysis of the recent SWEDEHEART registry publication [1], after reliably extracting the individual patient data, we demonstrated, in contrast to the original publication [1], a moderately high probability of increased mortality at 4 years among TAVR recipients who received a permanent pacemaker. The clinical importance is further emphasized by acknowledging the at least moderate chance that posterior probability for the mortality difference exceeds an absolute value of 1%.

This reanalysis should not be viewed as a criticism of the original analysis but rather as a complimentary addition to its pertinent research

question, rigorous design and data collection. As the original analysis used an 8-year follow-up window and as the hazard ratios varied over time, we analyzed the risk associated with a cardiac pacemaker using a shorter 4-year window. This has the advantages of being a period when the hazard ratios appear constant as well as providing results in a more clinically pertinent risk window. Certainly, one could argue that examining relative risks at 8 years when the mean entry age is 81 is of limited value since most patients will be deceased by this time, independently of the presence or absence of a pacemaker following their TAVR. A standard survival analysis using 4-year mortality as the outcome revealed an increased risk following pacemaker insertion (HR = 1.14, 95% CI 0.9–1.43) which not reach statistical significance ($p = 0.27$). However, the goal of this re-analysis was not to evaluate statistical significance but rather to estimate the probability of any increase in total mortality experienced by the pacemaker group. The estimation of this parameter requires a formal Bayesian survival analysis.

The Bayesian analysis with a vague prior revealed an 74.9% probability of increased mortality among TAVR patients requiring a pacemaker group compared those not requiring the same. The probability of increased mortality is augmented to 93.9–98.4% probability when informative prior knowledge about the risk of mortality with pacemakers in aortic stenosis patients undergoing SAVR is integrated as prior information into the decision calculus. This result was relatively robust as even a skeptical prior still resulted in a 70% probability of increased mortality following pacemaker insertion.

By concentrating on parameter estimation rather than on null hypothesis statistical testing and by incorporating relevant background knowledge, this Bayesian analysis arguably leads to a more insightful assessment of the risks of pacemakers following TAVR. Using aggregate data from previous clinical trials, multiple publications have demonstrated the additional advantages of Bayesian re-analyses [16,17]. The current article suggests that similar benefits may be observed when this approach is applied to individual patient data in the context of an observational research design.

Our study also has limitations. First, actual individual data was unavailable, which did not allow us to perform adjusted analysis with relevant covariates, limiting appropriate confounding control. Yet, we note that the frequentist results using extracted data from the reported Kaplan–Meier curve were very similar to the original paper. Thus, it is unlikely that a Bayesian analysis with actual individual data would yield highly different results compared to the ones reported in the present article. Second, because we limited our analysis to data extracted from Kaplan–Meier curves, we could only reanalyze the all-cause mortality

outcome. Third, these analyses were not preregistered; hence, they are exploratory and should be interpreted with caution. Lastly, we limited our analyses to a restricted number of priors and did not perform an extensive sensitivity analyses regarding our Bayesian analyses.

In conclusion, while the original publication concluded there was “no difference in long-term survival between patients who did and did not undergo permanent pacemaker implantation after TAVR,” this Bayesian reanalysis suggests a moderate to high probability that pacemaker implantation is associated with increased mortality in the first 4 years following TAVR.

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Declaration of Competing Interest

Both authors do not report any potential conflicts of interest.

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