**Title**:

Pacemaker Risk Following Transcatheter Aortic Valve Replacement - A Bayesian Reanalysis

**Running Title**:

Pacemaker Risk Following TAVR

**Authors**:

Arthur M. Albuquerque1 and James M. Brophy2

1 School of Medicine, Universidade Federal do Rio de Janeiro, Brazil; This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

2 McGill Health University Center, Montreal, Canada; This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

**Corresponding author**:

James Brophy MD PhD  
Professor of Medicine & Epidemiology (McGill University)  
McGill University Health Center  
1001 Decarie Blvd Room C04.1410  
Montreal (Qc) H4A 3J1  
e-mail: [james.brophy@mcgill.ca](mailto:james.brophy@mcgill.ca)

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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. There are several reasons to query the robustness of this analysis and to investigate if a Bayesian reanalysis would lead to the same conclusion.

Methods: A digitalized approach to the published Kaplan – Meier curves to permit the reconstruction of 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, and informative priors, based on the mortality risk of pacemaker implantation following surgical aortic valve replacement, were performed.

Results: Individual patient data was reliably extracted and showed an increased risk at 4 year follow-up (Hazard ratio (HR) = 1.08, 95% CI 0.85 - 1.36). The Bayesian analysis using a vague prior revealed a 75% probability of increased mortality in the pacemaker group. Using an informative prior, the posterior probability of increased mortality following pacemaker insertion was increased to 94%.

Conclusions: In contrast to the original publication, this Bayesian reanalysis suggests a moderate to high probability of an increased total mortality in TAVR patients following pacemaker implantation.

**Key Words**: Pacemaker, mortality, Bayesian

# Text

## 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). Leading the authors to conclude that long-term survival between patients who did and did not undergo permanent pacemaker implantation after TAVR was not different. While the study included a large unselected sample of 3,420 TAVR patients, there are a number of reasons why it is of interest to query the strength of the evidence supporting their conclusion.

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 post-TAVR. Thirdly, the same nationwide databases 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 understanding of this data and in presenting actionable probabilities.

## Methods

### 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 IPDfromKM (6) created this reconstruction of the individual patient data thereby allowing our secondary Bayesian survival analyses to be performed.

### 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.

### 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. These probability statements arise from the posterior distribution according to the following equation:

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 (7) through the R package rstanarm (8) . 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 coefficient regarding the risk of pacemaker exposure. 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 estimate pacemaker exposure’s marginal posterior distribution (log hazard ratio between pacemaker and no pacemaker groups), we used 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 an skeptical prior based on Placement of Aortic Transcatheter Valve Among (PARTNER) studies with patients at intermediate or high surgical risk who underwent TAVR (9). We extracted their 1-year mortality adjusted hazard ratio on pacemaker exposure to generate this prior (Normal [-0.01, 0.21]). Third, we used an informative prior (Normal[0.13, 0.094]) based on a previous study, using the nationwide Swedish databases as the article reanalyzed here (1), but in a cohort undergoing SAVR (2). We downweighted the influence of this informative prior by 50%, because while the populations are similar (everyone has aortic stenosis), 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, SAVR 50%). Lastly, we created a prior based on the same data, but with 100% of weight (Normal[0.13, 0.062]; hereafter, 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 (10). 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 >5%). We assumed a baseline mortality risk (no pacemaker group) of 39.9% at 4 years (11), 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>).

## Results

### 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 (Figure 1) with the published propensity-matched KM curve (Original Supplemental Figure 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).

The difference in survival probabilities with the 95% CI is plotted in Figure 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 (12).

### 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 0.9 - 1.43, p = 0.27. While this remains statistically not significant, the point estimate has clearly moved towards an increased mortality risk in the pacemaker group. Using this statistically non-sgnificant 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(13), we next explored the data with a Bayesian survival analysis.

### Bayesian survival analysis

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. Using a vague prior the 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 Figure 3 and Table 1, the use of a pacemaker is compatible with an 74.9% probability 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 (9), there is a apparent power increase, represented by the narrower credible interval (95% CrI 0.86 - 1.27), and smaller probability of increased mortality (Figure 3 and Table 1).

To further comprise other beliefs, we also reanalyzed this data using priors based on the same Swedish databases, but in patients undergoing SAVR (2). The choice for this belief was based on the similarities in the populations, everyone with aortic stenosis undergoing treatment in the same hospitals in the same treatment windows. With this informative prior downweighted by 50% (SAVR 50%), there is shift towards greater mortality association with pacemaker exposure (HR 1.12, 95% CrI 0.97 - 1.29), along with greater probability of HR > 1 (93.9%, Table 1). Without any downweight on the prior (SAVR 100%), the marginal posterior distribution shifts further from HR of 1 (Figure 3 and Table 1).

Another advantage of Bayesian analyses is the ability to calculate posterior probabilities other than of any harm (HR > 1), such as of 10% harm increase (HR > 1.10) or 25% increase (HR > 1.25). These posterior probabilities are shown for all beliefs in Table 1.

Lastly, to aid clinical decision-making, we estimated the marginal posterior distributions on risk differences (RDs). These distributions varied according to the underlying belief (Supplementary Table 1). The posterior probabilities of any harm on both relative (HR > 1.00, Table 1) and absolute scale (RD > 0%, Supplementary Table 1) are, as expected, identical. Moreover, we estimated the posterior probabilities of absolute mortality increase association with pacemaker exposure by 1% and 5%. The posterior probability of RD > 1% varied between 58.0% to 94%.

## Discussion

In this reanalysis of the recent SWEDEHEART registry publication(1), we were able to reliably extract the individual patient data concerning TAVR mortality as a function of receiving or not a permanent cardiac pacemaker. The original analysis used a 10-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 10 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. Our 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 an 93.9% probability when informative prior knowledge about the risk of mortality with pacemakers in aortic stenosis patients undergoing SAVR is integrated into the decision calculus.

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 (14, 15). 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 our 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.

# References

1. Ruck A, Saleh N, Glaser N. Outcomes following permanent pacemaker implantation after transcatheter aortic valve replacement: SWEDEHEART observational study. JACC Cardiovasc Interv 2021;14(19):2173–2181. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34620397>.

2. Glaser N, Persson M, Dalen M, Sartipy U. Long-term outcomes associated with permanent pacemaker implantation after surgical aortic valve replacement. JAMA Netw Open 2021;4(7):e2116564. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34255050>.

3. Gelman A, Carlin JB, Stern HS, Rubin DB. Bayesian data analysis. Third edition. Boca Raton: CRC Press; 2014:xiv, 661 pages. Available at: <Cover image http://images.tandf.co.uk/common/jackets/websmall/978143984/9781439840955.jpg>.

4. Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: Reconstructing the data from published kaplan-meier survival curves. BMC Med Res Methodol 2012;12:9. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22297116>.

5. R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2021. Available at: <https://www.R-project.org/>.

6. Liu N, Lee JJ. IPDfromKM: Map digitized survival curves back to individual patient data.; 2020. Available at: <https://CRAN.R-project.org/package=IPDfromKM>.

7. Stan Development Team. RStan: The R interface to Stan. 2021. Available at: <http://mc-stan.org/ 5>.

8. Brilleman SL, Elci EM, Novik JB, Wolfe R. Bayesian survival analysis using the rstanarm r package. 2020. Available at: <https://arxiv.org/abs/2002.09633>.

9. Arnold SV, Zhang Y, Baron SJ, et al. Impact of short-term complications on mortality and quality of life after transcatheter aortic valve replacement. JACC: Cardiovascular Interventions 2019;12(4):362–369. Available at: <https://www.sciencedirect.com/science/article/pii/S1936879818322970>.

10. McElreath R. Statistical Rethinking : A Bayesian Course with Examples in R and Stan. Chapman and Hall/CRC; 2020.

11. Skoetz N, Goldkuhle M, Dalen EC van, et al. GRADE guidelines 27: How to calculate absolute effects for time-to-event outcomes in summary of findings tables and evidence profiles. J. Clin. Epidemiol. 2020;118:124–131.

12. Austin PC. Statistical power to detect violation of the proportional hazards assumption when using the cox regression model. Journal of Statistical Computation and Simulation 2018;88(3):533–552. Available at: [https://doi.org/10.1080/00949655.2017.1397151]( https://doi.org/10.1080/00949655.2017.1397151).

13. Greenland S. Invited Commentary: The Need for Cognitive Science in Methodology. American Journal of Epidemiology 2017;186(6):639–645. Available at: <https://doi.org/10.1093/aje/kwx259>.

14. Brophy JM. Bayesian interpretation of the EXCEL trial and other randomized clinical trials of left main coronary artery revascularization. JAMA Intern Med 2020;180(7):986–992. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32478838>.

15. Goligher EC, Tomlinson G, Hajage D, 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 2018;320(21):2251–2259. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30347031>.

# Table 1

|  | | **Posterior probability, %** | | |
| --- | --- | --- | --- | --- |
| **Belief** | **HR (95% CrI)** | **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 |
| SAVR 50% | 1.12 (0.96, 1.27) | 93.9 | 57.9 | 5.6 |
| SAVR 100% | 1.13 (1.01, 1.26) | 98.4 | 66.7 | 3.1 |
| "SAVR 50%" regards posterior distribution while assuming a prior based on the surgical aortic valve replacement SWEDEHEART data with 50% of weight. "SAVR 100%" regards the same data, but with 100% weight. | | | | |
| Abbreviation: HR, hazard ratio | | | | |

# Figure Titles and Legends

Figure 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.

Figure 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.

Figure 3: Prior and Posterior Distributions of the Hazard Ratio (4-year time window)

Underlying prior and marginal posterior distributions regarding analyses restricted to 4-year time-window (Table 1). Panel A, Vague belief; B, Skeptical; C, SAVR 50%; D, SAVR 100%. Dashed lines depict the underlying 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.