**Title**:

Pacemaker Risk Following Transcatheter Aortic Valve Replacement - A Bayesian Reanalysis

**Running Title**:

Pacemaker Risk Following TAVR

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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 a 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 a high probability of increased total mortality in TAVR patients following pacemaker implantation.

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

**Condensed Abstract**: (27 words) A Bayesian reanalysis of a nationwide, population-based cohort of transcatheter aortic valve replacement patients suggests a moderate to high probability of increased total mortality following pacemaker implantation.

**Abbreviations List**: HR = hazard ratio; TAVR = transcatheter aortic valve replacement; SAVR = surgical aortic valve replacement; KM = Kaplan–Meier; CrI = credible interval

# 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, we used two different priors. First we performed the analysis using the rstanarm built-in default vague normal prior (Normal [0, 2.50]; mean and standard deviation). This prior contributes very little information to the posterior distribution and allows it to be completely dominated by the data. Next we used an informative prior (Normal[0.13, 0.094]) based on a previous study, using the same national databases, of pacemaker risk 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%.

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 (9).

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 (10).

### 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(11), we next explored the data with a Bayesian survival analysis.

### Bayesian surival analysis

Bayesian approaches to survival analysis can provide several 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 (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, the use of a pacemaker is compatible with an 75% probability of increased mortality compared to those not receiving a pacemaker.

Previously research using the same Swedish databases have examined the risk of a pacemaker in patients undergoing SAVR (2) and found an increased risk (HR 1.14; 95% CI, 1.01 - 1.29). Given the similarities in the populations, everyone with aortic stenosis undergoing treatment in the same hospitals in the same treatment windows, it seems reasonable to use this information, down weighted as described in the Methods, to represent our prior beliefs. With this informative prior, the HR for the no pacemaker group is 1.14, 95% credible interval (CrI 0.95 - 1.37). Given that this informative prior is consistent with the observed TAVR pacemaker data, the slight rightward shift and narrowing of the 95% CrI of the marginal posterior distribution compared to the marginal posterior with a vaguely informative prior is to be expected (Figure 3). Using this informative prior, it can be appreciated that the probability of increased mortality following a pacemaker post TAVR is 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 75% 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 94% 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 (12, 13). 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 analysis 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.

# Perspectives

What Is Known?

* Many patients undergoing TAVR require a permanent pacemaker. A recent study involving a large population-based cohort concluded that a pacemaker was not associated with increased mortality.

What Is New?

* This Bayesian reanalysis, using a shorter 4-year follow-up period, shows a modest to high probability of increased total mortality following pacemaker implantation

What Is Next?

* Prospectively planned Bayesian analyses of other datasets examining mortality and other clinically meaningful outcomes should be performed to confirm the reproducibility and generalizability of these findings.

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# 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: Data, Prior, and Posterior Distributions of the Hazard Ratio (4-year time window)

These figures show the underlying data along with Bayesian priors and marginal posterior distributions regarding analyses restricted to 4-year time-window. 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 (75% in Panel A, and 94% in Panel B). In both panels, “Data” regards the result from the frequentist Cox proportional hazards model restricted to 4-year time-window (HR = 1.14, 95% CI 0.9 - 1.43). Moreover, Panel A shows a vague, flat prior (HR = 1, 95% CI 0.01 - 134.29) along with the resulting marginal posterior distribution. Panel B shows the informative prior based on previous work, yet downweighted by 50% (HR = 1.14, 95% CI 0.95 - 1.37) along with the resulting marginal posterior distribution. Panel B may be used as our **central illustration**.