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Pacemaker Risk Following Transcatheter Aortic Valve Replacement - A Bayesian Reanalysis

Dear Professor Camici,

Thank you for your recent email. We would also like to thank the reviewers for their insightful comments and concerns. We have attempted to address them all and feel the manuscript has been substantially improved. Our replies are highlighted in bold.

Reviewer # 1

- The question is not whether frequentist or Bayesian is the best. Bayesian should be regarded as a complimentary technique which allows to better interpret the data based on prior information and/or beliefs. Furthermore, Bayesian approaches tend to be more intuitive and actionable for clinicians. In this regard, the manuscript reads too much as an attack on frequentist approaches and especially comes across as an outright critique on the Swedish study. I recommend lowering the tone and reformulating the manuscript as a complementary document that aims to help better interpret the findings of the Swedish study.

**Response: We completely agree with the reviewer’s sentiments that there is no place for inveterate antipathies concerning the different statistical paradigms. We certainly did not mean to minimize the work done by the Swedish group in posing their research question and assiduously collecting the required data. Our intention was to demonstrate the advantages that a Bayesian analysis brings to otherwise well performed research. We hope that this revision makes these points clearer.**

- The authors should be very careful not to bring frequentist statements in their own interpretation of the data. One example that stood out in the Abstract is the following sentence: "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)". Based on the large width of the credibility interval, this estimate does not allow to simply state that there was "an increased risk". Rather, the Bayesian conclusion from this should be that "the probability that permanent pacemaker implantation had any effect (HR>1) was 75% based on vague priors". Check and correct similar errors throughout the manuscript.

**Response: We agree with the reviewer that frequentist interpretations are generally unhelpful, even in the context of a Bayesian analysis. For a re-analysis to be useful, Bayesian or otherwise, one must first be certain that the original data has been accurately reproduced. Our Bayesian reanalysis is based not on aggregate data but on individual patient level data as abstracted from the original KM curves. Consequently, we reported our calculated frequentist result (Hazard ratio (HR) = 1.08, 95% CI 0.85 - 1.36) to demonstrate the comparability of our results with the original publication. "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)". As pointed out by the reviewer the CI does not permit the conclusion of an increased risk and we have corrected this to read "Individual patient data was reliably extracted as demonstrated by our ability to reliably reproduce the original results with a 4-year follow-up risk of Hazard ratio (HR) = 1.08, 95% CI 0.85 - 1.36".**

- The authors first criticize the Swedish study for using proportional hazards methods when the survival curves crossed (which might indeed be a sign that the propotional hazards assumption has been violated). Subsequently, in the Results they conclude that the proportional hazards test was not significant in the overall data. And eventually, they end up using proportional hazards methods themselves and report a global HR (although on data restricted to 4-year follow-up). To the reader, this comes across as if the authors made a 180° turn somewhere along the lines. I recommend revising this.

**Response: As we stated above, we report the isolated 4 year hazard ratio as a quality check as for data reproducibility ad this confirmed the original conclusions that the results was statistically non-significant. However, it is hopefully clear that we did not “make a 180° turn somewhere”. Rather by combining the probability of this observed data (likelihood function) with various prior beliefs we were able to calculate the posterior distribution of increased mortality. We have reviewed and revised the manuscript to make sure this key point is unambiguously stated.**

- It should be noted that defining the informative priors based on data from SAVR patients might have been inaccurate, as these represent a population that is distinct from the one undergoing TAVI and may subsequently have a different response to permanent pacemaker implantation. The authors used "downweighting" by increasing the standard error by 50%, however this is a method that only decreases precision / increases uncertainty but does not in any way change the mean effect size. Therefore, it would actually have been more interesting if the authors could have used a greater number of informative priors (similar to the skeptical, neutral, and enthusiastic as was used in the study by Goligher et al. [doi:10.1001/jama.2018.14276] that was cited by the authors themselves). In addition, informative priors based on a systematic review of prior studies could be implemented. This would allow them to define a range of probabilities for the question whether permanent pacemaker implantation increased the risk of death.

**Response: We agree with the reviewer that perfect exchangeability between the observed TAVR data and our choice of an informative prior (contemporary SAVR cases performed in the same institutions as the TAVR) cases can’t be proven, although the fact that both groups have the same underlying pathology, are being treated contemporaneously and in the same institutions is at least somewhat reassuring. We have further buttressed this opinion but now including a reference to a meta-analysis of 21 TAVR studies showing the same increased risk following pacemaker implantation. “Downweightling” increases the uncertainty by effectively decreasing the weight of the prior and consequently does lead to different posterior means as these are weighted means of the likelihood and the prior. Consequently, we believe our choice of a population with the same underlying population being treated at a similar time in the same institutions has merit in its choice as a base (neutral) case prior. We agree with the reviewer that the robustness of these conclusions can be strengthened by considering the impact of skeptical and enthusiastic priors which are now included.**

**As the goal of our paper is not to perform a systematic review of the subject but rather to demonstrate the added advantages of Bayesian inference, we referred to a very recent systematic review published in JACC(1) of 24 studies of TAVR patients receiving PPM. Based on this data, an enthusiastic (strong prior believer of increased pacemaker risk) prior is their reported result HR 1.17 (95% CI: 1.11–1.25). For a skeptical (strong prior believer of little or no pacemaker risk) prior, we refer to a recent publication from the PARTNER consortium (published after the JACC meta-analysis) that reported no increased mortality risk in TAVR patients requiring a pacemaker (HR 0.99 (0.65 to 1.49))(2).**

- The authors only reported the probabilities for the finding that permanent pacemaker implantation would have ANY effect (HR>1). However, it would be interesting if they could also provide probabilities for different HR cut-offs (>1.05, >1.10, >1.15, >1.20, etc...) and different absolute risk increase cut-offs (>1%, >2%, >5%, >10%, etc...). This is an aspect where the authors are not optimally using the Bayesian methodology, since using these different cut-offs provides a unique opportunity to extend the debate from "Is there any effect?" towards "How large of an effect may we expect?". Adding to this the various informative priors that I recommended in my prior comment, this paper could also address the question as to "Who may be at highest risk of poor survival following permanent pacemaker implantation?"

**Response: The reviewer makes an excellent point. While the probability of exceeding any specific threshold is always available from the area under the curve of the probability density function, in the revision we now explicitly present these results.**

- The term "TAVI" should be use: you are implanting a valve, not replacing it. The confusion that "TAVR" is came from the fact that it was used in Medicaid billing systems; however, it does not accurately reflect the actual procedure.

**Response: We have no skin in the TAVI versus TAVR name game. However, the original article we are commenting on used TAVR as has the most recent state of the art review article(1). Consequently, we have left TAVR in the manuscript but are open to the change to TAVI, if the editor so desires.**

Reviewer # 2

1. There is no reference in the first and second paragraphs of the statistical analyses section.

**Response: References have been added(3, 4)**

2. The statistical analyses should be reorganized, and more recent studies on imortance of bayesian in survival, difference between cox regression and bayesian, Such as,

Brard C, Le Teuff G, Le Deley MC, Hampson LV. Bayesian survival analysis in clinical trials: What methods are used in practice? Clin Trials. 2017 Feb;14(1):78-87

Soodejani MT, Tabatabaei SM, Mahmoudimanesh M. Bayesian statistics versus classical statistics in survival analysis: an applicable example. American Journal of Cardiovascular Disease. 2021;11(4):484.

**Response: While we thank the reviewer for the 2 references, we would point out that the importance of studies depends on more than their recency. Our goal for this paper is to show the added value of Bayesian methods, independent of any specific analysis such as survival analysis. Both of the suggested references emphasize that the value of Bayesian analyses depends on the use of prior information. We believe this concept is already conveyed by references(3, 4). Certainly, if the editor feels that these 2 additional references are also required, we will gladly include them.**

3. Describe in more detail how prior distributions are selected. Is the result better with a high standard deviation? Why was Normal(0,20) considered?

**Response: As outlined in our response to Reviewer #1, we have made substantial additions to the section on priors, emphasizing not only a wide clinically relevant choice but also the published scientific literature justifying their us. The default priors (Normal(0,20)) in the rstanarm package are chosen to “The default priors used in the various rstanarm modeling functions “are intended to be weakly informative so they can provide moderate regularlization and help stabilize computation” (https://mc-stan.org/rstanarm/).**

4.     The authors write in their Bayesian survival analysis section:

"The use of pacemaker is compatible with a 75% probability of increased mortality"

Would you please explain how you calculated 75 percent? and about 94% in this case:

"The probability of increased mortality following a pacemaker post TAVR is 94%"

**Response: These probabilities are calculated from the area under the posterior probability density functions. The explanation has been clarified in the revised submission.**

Reviewer # 3

1. The authors should also provide results of Bayesian analysis in terms of absolute risk difference to allow estimating probability of a clinically important increase in mortality, e.g., 1% to 5% increase in mortality. Currently the reported probability estimates are based on a >0% difference (HR >1). Also provide the extracted mortality event rates in the PM and no PM arms.

**Response: The suggested change has been incorporated in the revised manuscript.**

2. Exchangeability of SWEDEHEART SAVR and TAVR registries is key to justify borrowing of information. The more similar the 2 registries, the stronger the justification for borrowing. The SAVR Registry subjects are younger (69.7 vs 81.3y), less sick (for example a fib 16.2% vs 40.2%; HF 20.2% vs 43.5%; DM 18.9% vs 28.9%), with fewer women (36.9% vs 50.4%), and mean f/u is longer (7.3y vs 2.7y), thereby arguably questioning the justification for borrowing. The authors arbitrarily chose borrowing 50% weight from the SWEDEHEART registry to discount for any potential differences in baseline demographics. A more transparent way would be to show a sensitivity analysis of posterior probability across a range of prior weight (0 to 100%). This would help address the key question how much of the prior information needs to be borrowed to show a high posterior probability (>90%) of an increase in mortality with pacemaker.

**Response: As is often the case in Bayesian analyses, much of the discussion revolves around the choice of priors and not surprisingly this issue was also raised by Reviewers 1 and 2. We have greatly expanded the section of the choice of priors and provided literature references for our choices. The general robustness of our results to the choice of vague, mildly informative, skeptical or enthusiastic priors is reassuring.**

We hope that you will agree that the revised manuscript is improved and will be of interest to your readership.

Thank you again for your consideration.

Best regards,

James (Jay) Brophy MEng MD FRCP(c) FACC FCCS FCAHS PhD

Professor of Medicine & Epidemiology (McGill)

Centre for Health Outcomes Research (CORE)

5252 Boul. de Maisonneuve West Room 2B.37

Montreal  QC H4A 3S5

References

1. Sammour Y, Krishnaswamy A, Kumar A, Puri R, Tarakji KG, Bazarbashi N, et al. Incidence, Predictors, and Implications of Permanent Pacemaker Requirement After Transcatheter Aortic Valve Replacement. JACC Cardiovasc Interv. 2021;14(2):115-34.

2. Arnold SV, Zhang Y, Baron SJ, McAndrew TC, Alu MC, Kodali SK, et al. Impact of Short-Term Complications on Mortality and Quality of Life After Transcatheter Aortic Valve Replacement. JACC Cardiovasc Interv. 2019;12(4):362-9.

3. Brophy JM. Bayesian analyses of cardiovascular trials–bringing added value to the table. Canadian Journal of Cardiology. 2021.

4. Zampieri FG, Casey JD, Shankar-Hari M, Harrell FE, Jr., Harhay MO. Using Bayesian Methods to Augment the Interpretation of Critical Care Trials. An Overview of Theory and Example Reanalysis of the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial. Am J Respir Crit Care Med. 2021;203(5):543-52.

Arnold 3763 TAVR 326 need pacemaker mortality HR 1 year 0.99 (0.65 to 1.49) 0.99 (0.65 to 1.49)

3750 alive at 30 days