PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

Title (Provisional)

Prevalence and predictors of permanent pacemaker implantation in patients with aortic stenosis undergoing Transcatheter Aortic Valve Implantation: A Prospective Cohort Study

Authors

Wasim, Daanyaal; Ali, Abukar Mohamed; Bleie, Øyvind; Packer, Erik Jerome Stene; Eriksen, Erlend; Keilegavlen, Håvard; Rajani, Ronak; Rotevatn, Svein; Saeed, Sahrai

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VERSION 1 - REVIEW

Reviewer	**1**
Name	**Kopjar, Tomislav**
Affiliation	**University Hospital Centre Zagreb**
Date	**29-Sep-2024**
COI	**No competing interests.**

I would like to thank the authors for submitting their manuscript titled Prevalence and predictors of permanent pacemaker implantation in patients with aortic stenosis undergoing Transcatheter Aortic Valve Implantation: TAVI-NOR study to the BMJ Open journal. In their study authors aimed to identify predictors of new permanent pacemaker implantation in patients with severe aortic stenosis undergoing transcatheter aortic valve implantation. Originally, the patients were included in the TAVI-NOR study. The following comments are intended for your consideration.

1. The study is well written and illustrated.

2. It should be better clarified if the study is based on registry data or not? This is important for readers to be able to assess the degree of bias associated to database data.

3. Was the study registered in some international database? Since this it is claimed that this is a prospective study registration is mandatory as for any clinical trial. Acceptable registries for trials include clinicaltrials.gov.

4. Abstract, as well as the Strengths and limitations sections should be free of abbreviations.

5. Each abbreviation should be explained when first used (ie: RBBB: page 4, line 47)

6. The statistics section should be expanded to better describe the methods, including the multivariate regression.

7. How did you choose the variables for the univariate and multivariate analyses?

8. Several studies have already explored this topic. Try to emphasize what new information has been brought to light with this study.

9. Impact of PMI on long-term survival has been discussed in the manuscript accordingly.

10. I would suggest rewording the conclusion to read: Although PPMI after TAVI was not associated to mortality in this study, it should be interpreted with caution, since PPMI is a known marker for poor long-term outcome.

11. Changes in medical therapy compared to preimplantation could significantly impact study outcomes. How was this addressed during follow-up?

12. Read the instruction for authors carefully once again and reformat the manuscript accordingly.

13. There are some English language and grammar errors that need correcting. I kindly suggest a language review performed by a native speaker.

Reviewer	**2**
Name	**Kiani, Soroosh**
Affiliation	**UMass Chan Medical School Department of Medicine**
Date	**13-Nov-2024**
COI	**None to disclose.**

Well written manuscript detailing a prospective observational study of patients undergoing TAVI to assess risk of PMI.

1. The terms univariate/multivariate and univariable/multivariable are used seemingly interchanbably in the manuscript. In particular Multivariate and Multivariable regression are two distinct techniques and should be clarified. Based on the analysis described, it us assumed that the authors intended to use the latter. Please confirm and correct as necessary.

2. Was a stratified analysis done on the high and low volume phase? Do the models change when the data are stratified as such? While the phase is included as a variable in the model, multiple important factors (valve types, patient demographics and risk etc) all change between the phases. As such, the use of the phase a variable in the multivariable models, per se, may carry with more confounding that is apparent superficially.

The change in distributions in valve type alone (given that prosthesis expansion mechanism, generation etc have been associated with PMI), in addition to the anthropomorphic/demographic shift seems to warrant stratifying the models on study phase (which is albeit itself somewhat an artificial construct).

Moreover, if hte goal is to describe risk factors for PMI among patients undergoing TAVI, more contemporaneous data would be of greatest interest as it would be most generalizable to current practice. Given the above:

- Would the authors be willing to add additional analysis stratified on study phase (i.e., one model for the low volume phase, and one model for the high volume phase).

VERSION 1 - AUTHOR RESPONSE

Reviewer: 1

Dr. Tomislav Kopjar, University Hospital Centre Zagreb

Comments to the Author:

I would like to thank the authors for submitting their manuscript titled Prevalence and predictors of permanent pacemaker implantation in patients with aortic stenosis undergoing Transcatheter Aortic Valve Implantation: TAVI-NOR study to the BMJ Open journal. In their study authors aimed to identify predictors of new permanent pacemaker implantation in patients with severe aortic stenosis undergoing transcatheter aortic valve implantation. Originally, the patients were included in the TAVI-NOR study. The following comments are intended for your consideration.

1. The study is well written and illustrated.

Authors' response: We would like to thank the reviewer for the thorough evaluation of our manuscript and helpful comments and suggestions, which we believe raised the quality of our work.

2. It should be better clarified if the study is based on registry data or not? This is important for readers to be able to assess the degree of bias associated to database data.

Authors' response: Our study (TAVI-NOR) is a sub-study based on the nationwide, mandatory healthcare and quality improvement registry (Norwegian Registry of Invasive Cardiology (NORIC)) including all invasive cardiac procedures. All data in the present TAVI-NOR study was prospectively collected and quality assured through reviewing the electronic patient records. This design combines the strengths of a registry study and a prospective study design by using a structured registry

framework, while ensuring that data was systematically collected in real time. Hence, the following changes are made to better specify the study type (beginning of page 6):

Information on cardiovascular risk factors and comorbidities including hypertension, diabetes, hyperlipidemia and coronary artery disease (defined by findings of conventional coronary angiography or cardiac computed tomography, history of myocardial infarction, previous coronary artery bypass surgery or percutaneous coronary intervention) at baseline were obtained through the mandatory Norwegian Registry of Invasive Cardiology (NORIC) database. The data was prospectively collected and further quality assured through reviewing electronic patient records for the current TAVI-NOR study.

3. Was the study registered in some international database? Since this it is claimed that this is a prospective study registration is mandatory as for any clinical trial. Acceptable registries for trials include clinicaltrials.gov.

Authors' response: The study is indeed registered on clinicaltrials.gov and the identifier is added to page 5 and to the abstract.

4. Abstract, as well as the Strengths and limitations sections should be free of abbreviations.

Authors' response: As per your suggestion, we have removed abbreviations from the Strengths and Limitation section. However, the Editor suggested to explain abbreviations in the Abstract. For this reason, we have kept the two most used abbreviations (TAVI and AS) in order to reduce word count.

5. Each abbreviation should be explained when first used (ie: RBBB: page 4, line 47)

Authors' response: This has now been corrected.

6. The statistics section should be expanded to better describe the methods, including the multivariate regression.

Authors' response: We have expanded the Statistics section with some more details about the methodology, including the rational for choosing variables for the multivariable models (please see below in our response to comment 7).

7. How did you choose the variables for the univariate and multivariate analyses?

Authors' response to comment 6-7: Some sections were simplified to limit the total word count, but as the reviewer kindly points out our statistical section would benefit from elaborating on our approach. We are happy to add the following details that explain how we selected our uni-and multivariable models:

"Univariable and multivariable binary logistic regression analyses were performed to identify the predictors of PMI after TAVI. Multivariable models were adjusted for potential confounders and prognosticators based upon univariable associations or clinical relevance. Furthermore, we assessed for multicollinearity with the use of variance inflation factor testing (threshold <5). Only variables with minimal correlation were included in the multivariable model presented. Specifically, AF and overall abnormal ECG were not entered in the same multivariable model due to their high collinearity. Although the collinearity between RBBB and abnormal ECG was low, an abnormal ECG was a composite variable including the component of RBBB. For this reason, RBBB and AF were tested in separate models."

8. Several studies have already explored this topic. Try to emphasize what new information has been brought to light with this study.

Authors' response: Thank you for this important comment. We agree that prior studies have explored this topic. The novel features of the current study are that it represents a large sample of unselected patients with AS and examines temporal trends in permanent pacemaker implantation rates and the factors that may have contributed to any changes observed. This includes device iterations, operator experience and other heart rhythm abnormalities such as AF. The latter of which was largely ignored in prior studies. This new information has been added to the "Strength and Limitation of this Study" section as a new bullet point.

9. Impact of PMI on long-term survival has been discussed in the manuscript accordingly.

Authors' response: We appreciate this observation.

10. I would suggest rewording the conclusion to read: Although PPMI after TAVI was not associated to mortality in this study, it should be interpreted with caution, since PPMI is a known marker for poor long-term outcome.

Authors' response: As per the reviewer's recommendation this has now been amended:

Although pacemaker implantation after TAVI was not associated with all-cause mortality in this study, it should be interpreted with caution since pacemaker implantation has been suggested as a marker of poor long-term outcome in some other cohorts.

11. Changes in medical therapy compared to preimplantation could significantly impact study outcomes. How was this addressed during follow-up?

Authors' response: This information was not available. The following was added to the Limitations section:

Another limitation was that information on changes in medical therapy before and after PMI was unavailable.

12. Read the instruction for authors carefully once again and reformat the manuscript accordingly.

Authors' response: We appreciate the kind reminder and have thoroughly revised and updated the manuscript according to the journal format. We have included new sections such as "setting", statement of "patient and public involvement" and "trial registration" identifier.

13. There are some English language and grammar errors that need correcting. I kindly suggest a language review performed by a native speaker.

Authors' response: The manuscript has now undergone a further language review by a native speaker.

Reviewer: 2
Dr. Soroosh Kiani, UMass Chan Medical School Department of Medicine
Comments to the Author:
Well written manuscript detailing a prospective observational study of patients undergoing TAVI to assess risk of PMI.

1. The terms univariate/multivariate and univariable/multivariable are used seemingly interchangeably in the manuscript. In particular Multivariate and Multivariable regression are two distinct techniques and should be clarified. Based on the analysis described, it us assumed that the authors intended to use the latter. Please confirm and correct as necessary.

Authors' response: Thank you for the kind remarks and a thorough review of our manuscript. We agree that the correct terms here should be univariable and multivariable regression. This is also recommended by ASA (American Statistical Association). We have accordingly corrected these terms, now all read "multivariable".

2. Was a stratified analysis done on the high and low volume phase?

Authors' response: The most relevant phase would be the late high-volume phase, and the insights from this phase are better generalizable to the current practice. We have supplemented with stratified analysis. Thanks for this important comment.

Do the models change when the data are stratified as such?

Authors' response: The primary model did not change when stratified for study phases, please see supplementary tables showing multivariable models stratified by study phases. There were no changes in univariable analyses. To avoid presenting excessive information, we have provided only multivariable-adjusted models for the respected study phases in the same table (now Suppl. Table 4).

While the phase is included as a variable in the model, multiple important factors (valve types, patient demographics and risk etc.) all change between the phases. As such, the use of the phase a variable in the multivariable models, per se, may carry with more confounding that is apparent superficially.
The change in distributions in valve type alone (given that prosthesis expansion mechanism, generation etc. have been associated with PMI), in addition to the anthropomorphic /demographic shift seems to warrant stratifying the models on study phase (which is albeit itself somewhat an artificial construct). Moreover, if the goal is to describe risk factors for PMI among patients undergoing TAVI, more contemporaneous data would be of greatest interest as it would be most generalizable to current practice. Given the above:
- Would the authors be willing to add additional analysis stratified on study phase (i.e., one model for the low volume phase, and one model for the high volume phase).

Authors' response: Again, thank you for these important comments and suggestions. We have added a new supplementary table (Suppl. Table 4) with multivariable analyses stratified by study phases and implemented these results in the relevant section in the manuscript as well as updated the abstract (Objective section) to address this important point. The stratified results are largely in line with those presented for the entire study period (our original model - Table 4).

Other changes: We feel the following passage in the Introduction flows better with the Method section, with regard to criteria for PMI selection.
Current guidelines indicate PMI in those patients who have persistent/recurrent high-grad AV block 24-48 hour post TAVI and patients with pre-existing right bundle-branch block (RBBB) developing new post procedure conduction disturbances (10). Furthermore, expert consensus recommends PMI in those with PR prolongation/axis change, or persistent new-onset left bundle-branch block (LBBB) with QRS duration >150 ms or PR >240 ms (11).

Hence, we have moved this to the Methods with some changes in wording and added the following paragraph, page 7:
Patients received a PMI if they developed high-degree AV-block, pathological prolonged QRS duration with either RBBB or LBBB following TAVI by the discretion of treating physician based upon international guidelines (12-13).

Typo: Censoring date is 30.12.2022 (not 30.12.2023) - in line with our previous publications (PMID: 39536738). We have corrected this now.

Reviewer: 1 competing interests: No competing interests.

Reviewer: 2 competing interests: None to disclose.

VERSION 2 - REVIEW

Reviewer	**1**
Name	**Kopjar, Tomislav**
Affiliation	**University Hospital Centre Zagreb**
Date	**28-Dec-2024**
COI	

Thank you for resubmitting your work to the BMJ Open journal. Substantial changes were made to the manuscript. Overall scientific rigor and quality were improved. I have no further comments.