PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	ABO blood type and risk of porcine bioprosthetic aortic valve degeneration – SWEDEHEART observational cohort study
AUTHORS	Persson, Michael; Edgren, Gustaf; Dalén, Magnus; Glaser, Natalie; Olsson, Martin; Franco-Cereceda, Anders; Holzmann, Martin; Sartipy, Ulrik

VERSION 1 - REVIEW

REVIEWER	Philippe Pibarot Québec Hear & Lung Institute, Université Laval
REVIEW RETURNED	11-Feb-2019

GENERAL COMMENTS	Blood type A antigen on porcine aortic bioprostheses might initiate an immune reaction leading to an increased frequency of structural valve deterioration in patients with blood type B or O. The objective of this observational nationwide (Sweden) cohort study that included 3417 patients who underwent surgical AVR with a porcine bioprosthetic valve was to analyze the association between ABO blood type and porcine bioprosthetic aortic valve degeneration. The authors found no significant association between patient blood type and clinical manifestations of structural valve deterioration following porcine aortic valve replacement. These findings suggest that it is safe to use porcine bioprosthetic valves without consideration of ABO blood type in the recipient. This is a well-executed study and well written paper. Valve reoperation or hospitalization for heart failure may considerably underestimate the incidence of SVD. Recent position statement papers and standardized definitions (1,2) suggest to define SVD based on echo follow-up of prosthetic valve function. Do the authors have echo data in this cohort or at least in a sub-cohort. If yes, it would be very interesting to do analysis of SVD defined on the basis of echo parameters according to blood group. 1. Dvir D, Bourguignon T, Otto CM et al. Standardized definition of structural valve degeneration for surgical and transcatheter bioprosthetic aortic valves. Circulation 2018;137:388-399. 2. Salaun E, Clavel MA, Rodés-Cabau J, Pibarot P. Bioprosthetic aortic valve durability in the era of transcatheter aortic valve implantation. Heart 2018;104:1323-32.

REVIEWER	Dr Ashutosh Hardikar Department of Cardio-thoracic Surgery, Royal Hobart Hospital, Australia
REVIEW RETURNED	20-Feb-2019

GENERAL COMMENTS	Congratulations on handling one of the important questions in Structural valve deterioration [SVD]. It is a well presented paper with a large volume of cases from your national registry. My main concern is that although the title of the article deals with structural valve deterioration, your endpoints relate to re-operation, mortality or heart failure. To me, all those end points could well relate to small sized valves or patient-prosthesis mismatch as well. Are you able to confirm what were the indications for the re-operation and what percentage of the reoperations were for SVD? Also, there would be a significant proportion of patients who potentially have SVD and have not reached the endpoints that you were observing. How are we accounting for those patients? Once again, congratulations on a well written paper; but I feel that AV prosthesis size and Patient Prosthesis mismatch are important confounding factors which have not been addressed in your regression model.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1 Philippe Pibarot, Québec Heart & Lung Institute, Université Laval, Canada

Blood type A antigen on porcine aortic bioprostheses might initiate an immune reaction leading to an increased frequency of structural valve deterioration in patients with blood type B or O. The objective of this observational nationwide (Sweden) cohort study that included 3417 patients who underwent surgical AVR with a porcine bioprosthetic valve was to analyze the association between ABO blood type and porcine bioprosthetic aortic valve degeneration. The authors found no significant association between patient blood type and clinical manifestations of structural valve deterioration following porcine aortic valve replacement. These findings suggest that it is safe to use porcine bioprosthetic valves without consideration of ABO blood type in the recipient. This is a well-executed study and well written paper.

Response

Thank you very much for your detailed and thorough review of our paper.

1. Valve reoperation or hospitalization for heart failure may considerably underestimate the incidence of SVD. Recent position statement papers and standardized definitions (1,2) suggest to define SVD based on echo follow-up of prosthetic valve function. Do the authors have echo data in this cohort or at least in a sub-cohort. If yes, it would be very interesting to do analysis of SVD defined on the basis of echo parameters according to blood group.

1. Dvir D, Bourguignon T, Otto CM et al. Standardized definition of structural valve degeneration for surgical and transcatheter bioprosthetic aortic valves. Circulation 2018;137:388-399.

2. Salaun E, Clavel MA, Rodés-Cabau J, Pibarot P. Bioprosthetic aortic valve durability in the era of transcatheter aortic valve implantation. Heart 2018;104:1323-32.

Response

We agree that valve reoperation or hospitalization for heart failure may underestimate the true incidence of SVD. We acknowledge this limitation of our study in the manuscript under the subheading “Strengths and Limitations”.

We also agree that it would have been very valuable to have echo data in this study cohort in order to more accurately estimate SVD according to current standardized definitions as recommended by Dvir et al. Circulation 2018;137:388-399.

However, we reasoned that the clinical effects of valve degeneration would present as progressive heart failure due to stenosis or regurgitation, ultimately leading to reoperation or death. Unlike echocardiographic parameters, data on these outcomes (hospitalization for heart failure, aortic valve reoperation or death) are available for a large number of patients during a long follow-up in Swedish registries. Therefore, we used those outcomes as surrogates for clinically relevant SVD.

To further clarify and acknowledge that the findings of our study do not rule out a possible small or subclinical effect of patient blood group on the “true” rate of SVD (on the basis of echo parameters according to current guidelines), we added a sentence to the Discussion in the revised version.

The following text was added to the revised version of the manuscript (page 12):

“We lacked the necessary echocardiographic parameters to estimate the incidence of structural valve deterioration according to current standardized definitions,33 and therefore, our study cannot definitively rule out a possible small or subclinical effect of patient blood group on the true rate of structural valve deterioration.”

Reviewer #2: Dr Ashutosh Hardikar, Department of Cardio-thoracic Surgery, Royal Hobart Hospital, Australia

Congratulations on handling one of the important questions in Structural valve deterioration [SVD]. It is a well presented paper with a large volume of cases from your national registry.

Response

Thank you very much for your detailed and thorough review of our paper.

1. My main concern is that although the title of the article deals with structural valve deterioration, your endpoints relate to re-operation, mortality or heart failure. To me, all those end points could well relate to small sized valves or patient-prosthesis mismatch as well. Are you able to confirm what were the indications for the re-operation and what percentage of the reoperations were for SVD?

Response

As stated in our response to the comment from Reviewer #1, we agree that valve reoperation or hospitalization for heart failure may underestimate the true incidence of SVD. We acknowledge this limitation of our study in the manuscript under the subheading “Strengths and Limitations”. We also added a sentence to the discussion, please see our response to your comment #2 below.

Unfortunately, we do not have detailed information regarding the indications for the reoperation.

2. Also, there would be a significant proportion of patients who potentially have SVD and have not reached the endpoints that you were observing. How are we accounting for those patients?

Response

The current standardized definition of SVD for surgical aortic valves require echo parameters not available in Swedish national health-data registers or the SWEDEHEART register. Therefore, we had to rely on surrogate endpoints and this is acknowledged as a limitation of our study in the manuscript under the subheading “Strengths and Limitations”.

We agree that it would have been very valuable to have echo data in this study cohort in order to more accurately estimate SVD according to current standardized definitions (Dvir et al. Circulation 2018;137:388-399).

As stated in our response to Reviewer #1, we added a sentence to the Discussion in order to clarify and acknowledge that the findings of our study do not rule out a possible small or subclinical effect of patient blood group on the “true” rate of SVD (on the basis of echo parameters according to current guidelines).

The following text was added to the revised version of the manuscript (page 12):

“We lacked the necessary echocardiographic parameters to estimate the incidence of structural valve deterioration according to current standardized definitions,33 and therefore, our study cannot definitively rule out a possible small or subclinical effect of patient blood group on the true rate of structural valve deterioration.”

3. Once again, congratulations on a well written paper; but I feel that AV prosthesis size and Patient Prosthesis mismatch are important confounding factors which have not been addressed in your regression model.

Response

Thank you for a thorough review and constructive criticism of our manuscript. Although we agree that the literature reports both valve size and PPM as risk factors for SVD, we disagree that they are factors that should be included in the regression model. The reason is that it is highly unlikely that factors such as implanted valve size or PPM would be related to patient blood group. These factors are therefore by definition not “confounding factors”, and should not be adjusted for in a multivariable regression model.

In the manuscript, under the subheading “Strengths and Limitations”, we briefly discuss why this study may be regarded as a natural experiment and that the crude (unadjusted) estimates of the association between exposure (blood group) and outcome (reoperation, heart failure, or death) would be valid. This is corroborated by the fact that we found only small changes in the point estimates after multivariable adjustment.

VERSION 2 – REVIEW

REVIEWER	Philippe Pibarot Québec Heart & Lung Institute
REVIEW RETURNED	18-Mar-2019

GENERAL COMMENTS	The authors have well responded to my previous comments.

REVIEWER	Dr Ashutosh Hardikar Royal Hobart Hospital Australia
REVIEW RETURNED	17-Mar-2019

GENERAL COMMENTS	It is a well structured study to answer an important question. Is there any data available on the mechanism of heart failure in terms of how many were aortic stenosis and how many were aortic regurgitation? Also, in what % was infective endocarditis a cause of heart failure?

VERSION 2 – AUTHOR RESPONSE

Reviewer #1 Philippe Pibarot, Québec Heart & Lung Institute, Université Laval, Canada

The authors have well responded to my previous comments.

Response

Thank you very much for again taking time to critically review our paper.

Reviewer #2: Dr Ashutosh Hardikar, Department of Cardio-thoracic Surgery, Royal Hobart Hospital, Australia

It is a well structured study to answer an important question. Is there any data available on the mechanism of heart failure in terms of how many were aortic stenosis and how many were aortic regurgitation? Also, in what % was infective endocarditis a cause of heart failure?

Response

Again, thank you very much for your detailed and thorough review of our paper.

Unfortunately, echo parameters were not available from the Swedish national health-data registers or the SWEDEHEART register that were used as data sources for the current study. Therefore, we are unable to provide further information regarding the mechanism of heart failure (aortic stenosis, regurgitation or endocarditis). This was also stated in our previous “Response to Reviewers’ comments” letter, and text was added to the revised manuscript to acknowledge this limitation of our study.