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Reviewer A

1. Comment: Hemorrhagic / thromboembolic complications are trade-off of the reoperation in comparisons between biologic and mechanical valve replacement. As the reoperation is analyzed, I also wonder how the Hemorrhagic / thromboembolic risks differ between groups.

Answer: We agree with the reviewer. We have now added information about long-term hemorrhagic risk and thromboembolic complications (stroke and myocardial infarction) in a new Table 4, which also contains event rates and unadjusted and hazard ratios from unadjusted and adjusted Cox regression models.

Changes: A new Table 4, page 24, has been added. The results are also presented in the Results section, page 11, line 1-9. The sentences read: "Number of events, events per 100 patient years, and unadjusted and adjusted hazard ratios for deaths, aortic valve reoperations major bleeding, ischemic strokes and myocardial infarction during follow-up are presented in Table 4. During follow-up, ten out of 335 patients (2.1%) were reoperated on the aortic valve, 6/253 (2.4%) in the bAVR group and 4/82 (4.9%) in the mAVR group. A Kaplan-Meier plot of the reoperations is presented in Supplementary figure 2. Three of the reoperations in the bAVR group were a TAVI. There were no significant differences in the adjusted risk for any of the reported events between the bAVR and mAVR group."

2. Comment: Reoperation events were merely compared as frequencies without a regard to time factor, but this needs more adequate investigations through Kaplan-Meir method (crude), Cox -proportional models (adjusted) and more idealistically competing risk model (such as Fine-Gray model). I would recommend to do so also on the hemorrhagic events.

Answer: We have now presenting the unadjusted hazard ratios for reoperation in the new Table 4 and added a Kaplan-Meier analysis of reoperations in the two groups. However, the total number of reoperation events (n=10) is too small to make any multivariable analyses.

Changes: The unadjusted hazard ratio is presented in the new Table 4. A Kaplan-Meier figure has been added to the manuscript as Supplementary figure 2 and are referred to on page 9, line 1,2.

We have also revised the Results section on page 11, line 61 -9, which now reads: "Number of events, events per 100 patient years, and unadjusted and adjusted hazard ratios for deaths, aortic valve reoperations major bleeding, ischemic strokes and myocardial infarction during follow-up are presented in Table 4. During follow-up, ten out of 335 patients (2.1%) were reoperated on the aortic valve, 6/253 (2.4%) in the bAVR group and 4/82 (4.9%) in the mAVR group. A Kaplan-Meier plot of the reoperations is presented in Supplementary figure 2. Three of the reoperations in the bAVR group were a TAVI. There were no significant differences in the adjusted risk for any of the reported events between the bAVR and mAVR group".

3. **Comment: It is well-known that mechanical valve replacement inevitably carries risks of hemorrhagic / thromboembolic complications, and therefore, if the survival and reoperation estimates are given equal, should bio-valves be preferred option for patients on dialysis from a view of quality of life? Please elaborate authors' thoughts on this issue.**

Answer: In our manuscript we suggest that a biological prosthesis is an adequate valve choice in most dialysis patients. The possibility to avoid systemic anticoagulation represent one of the advantages of biological prosthesis that may affect positively to the patient´s quality of life. A brief comment has been added to the text.

Changes: The sentence on page 13, line 2,3 reads: "In addition, the avoidance of systemic anticoagulation may have positive impact on the patients' quality of life".

Reviewer B

1. Comment: The period covered by this observation is a long one, 20 years, but has there been any change in the strategy for aortic valve replacement at your institution?

Answer: Over the years we have followed the recommendations in international guidelines, but otherwise no institutional guidelines has been changed.

Changes: None

2. Comment: Also, bioprosthetic valves have evolved rapidly in the past 20 years. Surgical outcomes and mid-term prognosis have not changed, but have improved prosthetic valves had any impact on long-term outcomes?

Answer: We understand the reviewer's point but unfortunately, the study sample is too limited to answer this question. In addition, the follow-up time for the prostheses used during the last years is still limited. We have added this issue to the limitation paragraph

Changes: The sentence in the limitations paragraph on page 14, line 16,17, reads: "Furthermore, improvements of valve prostheses over the years may impact the results".

3. Comment: If we assume that the prognosis for dialysis is ten years, would it be better to limit the cases to those from 2007 to 2017 so that there is a more negligible difference in the quality of the bioprosthetic valves?

Answer: If we restrict the analysis only to the patients operated on 2007- 2017, the total number of patients included in the study would too small for statistical comparisons and to make any meaningful conclusions. We have, as mentioned above, added that the quality of the prostheses may differ over time as a limitation in the study.

Changes: The sentence in the limitations paragraph on page 14, line 16,17, reads: "Improvements of valve prostheses may impact the results".

4. Comment: It is well known that dialysis patients with a history of diabetes, heart failure, and cancer have low 5-year survival rates. You also commented in your discussion about what happens after kidney transplantation. Therefore, I don't understand which valve you would recommend for such cases.

Answer: We agree with the reviewer that it is difficult to make any firm recommendations in patients that will, or had, undergone kidney transplantation, especially if they have other risk factors. One would suspect that the chronological age is lower and life expectancy is longer than average in these patients and thus a

mechanical valve may be a reasonable choice. This point of view is stated on page 13 line 5-9. "In cases where dialysis patients are deemed to be candidates for future kidney transplantation, the use of a mechanical valve may be considered because of the prolonged long-term survival after kidney transplant in patients with end-stage renal disease". We agree with the reviewer that this is speculative and that we have no firm evidence from the present study to support this statement.

Changes: None

5. Comment: This study shows that the prognosis is so poor in dialysis patients that it makes no difference which valve is used. Are you trying to tell us that it is acceptable to use a bioprosthetic valve in such cases?

Answer: What we are trying to do is reporting outcome after aortic valve replacement with either a bioprosthesis or a mechanical prosthesis in a national cohort of dialysis patients. In addition, we are discussing possible interpretations of the results. We did find an overall cumulative survival of only 51% at five years and even lower in patients with heart failure and/or diabetes (Fig 3 and Fig 4). Our interpretation is therefore that for most patients a biological valve is an adequate choice, as stated in the conclusions of the manuscript, page 14, line 22-24. However, we are also stating that for selected patients e.g. those who are deemed to be candidate for kidney transplant and young patients with few or almost no comorbidities, a mechanical valve is a reasonable choice. In our opinion, the present data does not allow any firmer conclusions.

Changes: None

6. Comment: If we analyze the distant prognosis based on all-cause mortality, the type of prosthetic valve becomes irrelevant to the prognosis, and the effectiveness of the prosthetic valve function itself cannot be demonstrated.

Answer: We agree with the reviewer. The present study does not demonstrate the superiority of any of the valve types. Unfortunately, we do not have echocardiography to assess structural valve deterioration.

Changes: None

7. Comment. If there is no follow-up echocardiography to show the prosthetic valve function, do you have an alternative indicator of heart failure? In addition,

I think it is necessary to investigate cerebral complications such as bleeding and embolization for the remote prognosis of mechanical valves, but do you have any observational data?

Answer: Unfortunately, we do not have any data on alternative methods to assess heart failure, such as NT-ProBNP levels or ejection fraction over time. We agree with the reviewer about bleeding and thromboembolic complications and have added data about this in the new Table 4, as also suggested by reviewer A.

Changes: Changes: A new Table 4 has been added. The results are also presented in the Results section, page 11, line 1-9. The sentences read: "Number of events, events per 100 patient years, and unadjusted and adjusted hazard ratios for deaths, aortic valve reoperations major bleeding, ischemic strokes and myocardial infarction during follow-up are presented in Table 4. During follow-up, ten out of 335 patients (2.1%) were reoperated on the aortic valve, 6/253 (2.4%) in the bAVR group and 4/82 (4.9%) in the mAVR group. A Kaplan-Meier plot of the reoperations is presented in Supplementary figure 2. Three of the reoperations in the bAVR group were a TAVI. There were no significant differences in the adjusted risk for any of the reported events between the bAVR and mAVR group."

Reviewer C

1. Comment: I suggest listing inclusion/exclusion criteria in a CONSORT flow diagram as either a figure or supplemental figure. Was endocarditis excluded?

Answer: We have added a flow chart, as Supplementary figure 1, as suggested by the reviewer. Patients with endocarditis were excluded.

Changes: See above. We have clarified on Supplementary file page 8, line 1, and manuscript page 6, line 6-9, that patients with endocarditis were excluded.

2. Can you clarify "preoperative dialysis"? Did 100% of patients have a diagnosis of "end stage renal disease" or is it possible a patient had one episode of dialysis prior to surgery? I'm assuming 100% ESRD, but this could be made more clear in the methods section.

Answer: All the patients enrolled in the study had ESRD with preoperative dialysis.

This is now clarified in the manuscript

Changes: The sentence on page 6, line 3-6 now reads: "All 335 patients ≥18 years with endstage renal disease and preoperative dialysis who underwent a first surgical implantation of a biological (bAVR) or a mechanical (mAVR) aortic valve prosthesis, isolated or in combination with CABG, from 1997 to 2017 in Sweden were included in a registry-based longitudinal cohort study".

3. Do you believe your study is sufficiently powered to detect a difference in the matched cohort? If not, does that undermine your conclusion that tissue valve is the best choice in all ESRD patients?

Answer: We thank the reviewer for this important comment. A larger study population would have been desirable, but as stated in the manuscript we included all eligible patients in Sweden during a 21-year period. A longer inclusion period would increase the number of patients but add other bias due to changes in medical treatment etc. Our main findings, i.e. no significant difference between tissue valves and mechanical valves in dialysis patients, corroborates the much larger meta-analysis in ESRD patients (n=8438), which in contrast to the present manuscript included different valve replacement procedures (Phan et al J Thorac Dis 2016). This publication is referenced in the manuscript.

We do not state anywhere in the manuscript that "tissue valve is the best choice in all ESRD patients". Instead, we propose that a bioprosthesis is an adequate choice for most ESRD patients, as stated in the conclusions of the manuscript, page 14, line 22-24. However, we are also stating that for selected patients, e.g. those who will undergo kidney transplant and young patients with few or almost no comorbidities, may be candidates for implantation of a mechanical valve. In our opinion, the present data does not allow any firmer conclusions.

Changes: None

4. Comment: The median age of the tissue valve group was 70 years, most of whom would undergo TAVR in the current era. Can the authors extrapolate how their study's findings impact TAVR vs SAVR decision making in these patients?

Answer: We agree that many of those patients would undergo TAVR in the current era, given their high surgical risk. In our opinion, the present study gives no

information about the choice between SAVR and TAVI

Changes: None

5. Some surgeons/cardiologists advocate for mechanical AVR in ESRD patients due to concern of early SVD in this patient cohort. Can the authors comment in the discussion regarding this point? They note that SVD is not identified in the analysis and given the median f/u is 2.8 years, perhaps the conclusion that tissue valve is the best choice may be premature based on the data and analysis.

Answer: We acknowledge that the lack of information about SVD is a major limitation of the present study. What we know is that only 6/253 patients (2.4%; 0.7 reoperations per 100 patient years) in the bAVR group was reoperated with either SAVR or TAVI during the follow-up period. This argues against that severe SVD, necessitating reoperation, occurs early after the operation. Numerically, reoperation was in fact more common in mAVR patients (4/82, 4.9%; 1.1 per 100 patient years). We agree that this data does not exclude accelerated SVD and have now extended the present discussion about this in the limitation paragraph, as suggested by the reviewer.

Changes: The extended discussion on page 14, line 10-17 reads: “Lack of access to any echocardiographic follow-up limits the more detailed study of structural valve deterioration in the biological valve group. However, reoperations in the bAVR group were sparse, only 2.4% of the patients underwent reoperations with either SAVR or TAVI during the limited follow-up period. This argues against that severe SVD, necessitating reoperation, occurs early after bAVR in dialysis patients. Numerically, reoperations were in fact more common in mAVR patients (4.9%).”