

## Peer review file

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### Reviewer A

#### ▶ Comment 1

In the present manuscript by Kim W. et al also aims evaluate clinical outcomes of those who receive bovine pericardial and porcine types of mitral valve. The study endpoints include overall survival and incidence of bioprosthetic valve dysfunction. The study analysis was performed with proper statistical methods which supported the study conclusion. However, the authors did not include the analysis of valve-related complications such as valve thrombosis, types of SVD, infection, etc. Due to the lack of in-depth analysis on SVD, the study may add limited clinical knowledge on mitral bioprosthetic valve.

#### ▷ Reply 1

Thank for your valuable comments. We added detailed information regarding valve-related complications including thrombosis and endocarditis. In addition, lack of in-depth analysis on SVD was discussed as a limitation of this study.

#### ▷ Changes in the text 1

<**Results**> MV reoperations were performed in 34 patients, including 18 reoperations for SVD, which composed of 11 reoperations in the BMVR group and 7 in the PMVR group. Prosthetic valve thrombosis occurred in 8 and 3 patients in the BMVR and PMVR groups, respectively. CTEB occurred in 40 (12.9%) patients during follow-up (32 and 8 in the BMVR and PMVR groups, respectively). There were no differences in the cumulative incidence of CTEB between the 2 groups (P=0.66). Prosthetic valve endocarditis occurred in 5 and 3 patients in the BMVR and PMVR groups, respectively, without intergroup difference (P=0.30).

#### <**Discussion**>

Third, in-depth analysis regarding the SVD were limited due to a retrospective nature of the present study; both stenosis and regurgitation of the prosthetic valve were treated as the same SVD and hemodynamic consequence and clinical physical status of patients with SVD were not analyzed further.

#### ▶ Comment 2

Page 3, lines 65-71: Base on STROBE statement 13+(c): Please provide a diagram of the patient enrollment, allocation, follow up and analysis.

▷ Reply 2

As Reviewer indicated, we added the diagram of study patients.

▷ Changes in the text 2

<**Patients and Methods**> This study complied with the Declaration of Helsinki. From January 2001 to December 2018, 1156 patients underwent MVR at our institution. Of these patients, 814 who underwent MVR with mechanical valves and 33 who underwent MVR with other types of tissue valves were excluded. A total of 309 patients who underwent MVR with Carpentier-Edwards PERIMOUNT bovine pericardial valves (Edwards Lifesciences, Irvine, CA, USA; BMVR group, n = 241) or Hancock II porcine bioprosthesis (Medtronic, Inc., Minneapolis, MN, USA; PMVR group, n = 68) were enrolled (Figure 1).

<**Figure Legends**> **Figure 1: Flowchart of the patient selection process. MVR, mitral valve replacement; BMVR, mitral valve replacement with Carpentier-Edwards PERIMOUNT bovine pericardial valves; PMVR, mitral valve replacement (MVR) with Hancock II porcine bioprostheses.**

▶ Comment 3

Page 4 lines 99-102: The authors describe in discussion that this study define SVD in accordance with the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) guideline released in 2017. The author should cite the reference here. However, the criteria of pressure gradient over 6mmHg does not appear in the guideline.

▷ Reply 3

As Reviewer indicated, we added the reference at “Patients and Methods” and “Discussion” section.

In addition, we added other guidelines showing the criteria of pressure gradient over 6mmHg for prosthetic mitral valve function as reference #6.

▷ Changes in the text 3

<**References**>

6. Zoghbi WA, Chambers JB, Dumesnil JG, et al. recommendations for evaluation of prosthetic valves with echocardiography and doppler ultrasound. *J Am Soc Echocardiogr* 2009;22:975-1014.

► Comment 4

Early technical failure and endocarditis were excluded from this study. Please explain the reasoning. In Table 1, there are 11.2 (BMVR) and 13.2 % (PMVR) of patients who had the diagnosis of endocarditis. Why these cases were not excluded as described in the methods?

▷ Reply 4

There were text errors as the reviewer commented. We corrected these errors to avoid any confusion.

▷ Changes in the text 4

<Evaluation of early and long-term clinical outcomes> SVD was defined as intrinsic changes to the xenograft, such as leaflet thickening, calcification, and tear, leading to mitral stenosis with the mean pressure gradient over 6 mmHg or mitral regurgitation of greater than **or equal to moderate degree (4-6). Changes in echocardiographic data such as increase of mean pressure gradient or regurgitation due to prosthetic valve endocarditis was excluded.** The diagnosis of SVD relied on the aspects of the valve at reoperation and on echocardiographic surveillance.

▣ Comment 5

Page 6, line 162: how many reoperations for SVD were in BMVR and PMVR groups, respectively?

▷ Reply 5

There were 11 reoperations for SVD in BMVR group and 7 reoperations in PMVR group. We added these results in the text.

▷ Changes in the text 5

<Long-term mitral valve-related events> MV reoperations were performed in 34 patients, including 18 reoperations for SVD, **which composed of 11 reoperations in the BMVR group and 7 in the PMVR group.**

▣ Comment 6

Page 7, line 173: There is also a role for mitral replacement for patients with functional mitral regurgitation.

▷ Reply 6

As Reviewer indicated, we corrected sentences and added a reference as reference #9.

▷ Changes in the text 6

<**Discussion**> Although MV repair has been widely adopted for the surgical treatment of MV disease, MVR remains a viable option for patients with rheumatic MV disease **and those with functional mitral regurgitation (7-9).**

<**References**>

9. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2021 2;143:e35-71.

▣ Comment 7

Page 8, lines 203-205: As stated in Ref. 18, the predominant cause of SVD was degeneration in bovine pericardial valve, while it was combined degeneration and leaflet tear in porcine type of valve.

▷ Reply 7

We revised lines 203-205 as the reviewer indicated.

<**Discussion**> **A previous study suggested that degeneration in bovine pericardial valve, while it was combined degeneration and leaflet tear in porcine type of valve**

## **Reviewer B**

▣ Comment 1

One question. There was not significantly difference between two valves. What is the point to choose either valve in patients aged at 65 years? Is it just surgeons' preference? Is there any suggestion as to valve choice based on the current study?

▷ Reply 1

Thank you for your comment. As described at “Operative data” of “Patients and Methods” section, the selection of the valve was at the discretion of the attending surgeons in the present

study. It is still the same based on the similar long-term results after bioprosthetic MVR using these valves.

▷ Changes in the text 1

We added a sentence at “Conclusion” section.

<Conclusion>

Surgeons could select either prosthesis based on their own experiences.

### Reviewer C

▣ Comment 1

In the title, only structural valve deterioration (SVD) is mentioned. However, the review focuses on clinical outcomes after mitral valve replacement using PMVR and BMVR. Please rephrase, so survival is not left out in the title of the study.

▷ Reply 1

We revised the title of this manuscript.

▷ Changes in the text 1

<Title> Comparative analysis of structural valve deterioration and long-term clinical outcomes after bovine pericardial versus porcine bioprosthetic mitral valve replacement

▣ Comment 2

Please revise word choice, grammar and sentence structure. Parts of the manuscript seem rather unpolished language wise.

▷ Reply 2

As Reviewer indicated, we revised English correction once again. Certificate for the correction was attached.

▶ Comment 3

Risk factors for overall survival, SVD and mitral valve related events as shown in tables 3-5 were not reported in the results or discussion section. Please describe and discuss these results.

▷ Reply 3

As Reviewer indicated, we added the results about risk factors and discussed about that. Especially, we added the discussion of the Euroscore II.

▷ Changes in the text 3

<Long-term survival> There were no significant differences in the overall survival rates and cumulative incidences of cardiac death between the two groups (P = 0.59 and 0.15, respectively; Table 3 and Figure 2). Risk factors associated with overall survival in the multivariable analysis were age, dyslipidemia, NYHA class  $\geq 3$ , LV dysfunction, Euroscore II and arrhythmia surgery (Table 3).

<Long-term mitral valve-related events> The competing risk analysis demonstrated that the cumulative incidence of SVD was not significantly different between the two groups (P=0.23; Table 4 and Figure 3). Euroscore II was associated with SVD in the multivariable analysis (Table 4).

<Long-term mitral valve-related events> There was no significant difference in the cumulative incidence of MVRE between the two groups (P=0.065; Table 5 and Figure 4). Risk factors associated with MVRE in the multivariable analysis were NYHA class  $\geq 3$  and Euroscore II (Table 5).

<Discussion> The risk factor analyses showed that Euroscore II was a factor associated with various events after MVR including overall survival, SVD and MVRE. Euroscore II is a well-known evaluation tool to predict early mortality after cardiac surgery (21). The present study showed that the Euroscore II also reflected long-term survival after bioprosthetic MVR. Contrary to survival and MVRE, Euroscore II had negative correlation with SVD. This might be due to high probability of death in patients with high Euroscore II, which masked the risk of SVD, although competing risk analysis were performed.

► Comment 4

Definition of exclusion criteria (line 105): please define if you mean early endocarditis following the procedure or endocarditis as indication for mitral valve operation.

▷ Reply 4

There were text error as the reviewer commented. We corrected this error to avoid any confusion.

▷ Changes in the text 4

<Evaluation of early and long-term clinical outcomes> SVD was defined as intrinsic changes to the xenograft, such as leaflet thickening, calcification, and tear, leading to mitral stenosis with the mean pressure gradient over 6 mmHg or mitral regurgitation of greater than or equal to moderate degree (4-6). Changes in echocardiographic data such as increase of mean pressure

gradient or regurgitation due to prosthetic valve endocarditis was excluded. The diagnosis of SVD relied on the aspects of the valve at reoperation and on echocardiographic surveillance.

► Comment 5

Definition of SVD (lines 100-102): did you mean “greater than or equal to” moderate or do you not consider moderate regurgitation SVD?

▷ Reply 5

As Reviewer indicated, we corrected it as “greater than or equal to”.

► Comment 6

Conclusion: Please be more precise in the phrasing of your conclusion.

▷ Reply 6

We revised conclusion as the reviewer recommended.

▷ Changes in the text 6

<**Conclusion**> The clinical outcomes including overall survival, SVD and MVRE after bioprosthetic MVRs using Carpentier-Edwards bovine pericardial and Hancock II porcine valves might not be significantly different for, on average, 7 years of clinical follow-up. Surgeons could select either prosthesis based on their own experiences.

► Comment 7

Supplement Table 2: Please refine the term “Bleeding reoperation”. In line 142-143 you refer to this as “reoperation for bleeding”. E.g. “reoperation due to bleeding” would be much easier to understand.

▷ Reply 7

As Reviewer indicated, we corrected the words.

► Comment 8

Figure 1, 2 and 3: Please add the number of patients at risk for each group at the different time points.

▷ Reply 8

We revised the figures as reviewer indicated.

► Comment 9

STROBE Statement: the column “Reported on Section/Paragraph” in the supplements is not cut off in various lines. Please correct, so all information is readable.

▷ Reply 9

As Reviewer indicated, we corrected STROBE statement.