Peer review file

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Reviewer A

Comment 1: 15% of the AVR were size 19/21mm and 30% were size 23mm. These are small valve sizes (especially the 19/21mm group) which would present future difficulties with transcatheter aortic valve deployment with degeneration and would necessitate redo-open surgical AVR for future intervention. There is a recent push to place larger bioprosthetic valves particularly with root enlargement or other root procedures. Has the authors used root enlargement for these procedures?

Reply 1: During the present investigation's implantation interval (10/2007-09/2008) of the Perimount Magna Ease prosthesis (PME), clinical implementation of TAVR was just starting. Thus, at that time there was not such a push to initially place larger bioprosthetic valves during surgical aortic valve replacement (SAVR), particularly with root enlargement, facilitating future valve-in-valve TAVR. Aortic root enlargement increases the extent of the operation. Furthermore, it bares potential risk of bleeding at the site of the root enlargement which can be difficult to manage. Consequently, the risks and benefits of this procedure need to be thoroughly contemplated. In the patients of the present investigation no aortic root enlargement or other root procedures were performed during PME implantation.

Changes in the text: We added to the discussion "In young patients and patients with small aortic annulus who are at risk for future reintervention due to SVD, aortic root enlargement in combination with SAVR facilitating the implantation of a larger prosthetic valve should be kept in mind. In the meta-analysis by Yu et al. aortic root enlargement was found to be a safe adjunct to SAVR resulting in larger implanted prosthetic valves and less PPM possibly improving future valve-in-valve TAVR outcomes (19). They could also show that addition of aortic root enlargement to SAVR does not increase early adverse events such as myocardial infarction, permanent pacemaker implantation, reoperation for bleeding, or stroke. However, aortic root enlargement increases the extent of the operation resulting in increased aortic cross-clamp time which was associated with increased late mortality (20). In the present study, none of the patients received aortic root enlargement." (see **Page 10, Lines 235, 236, Page 11, Lines 237-245**).

Comment 2: The increased late AV gradients with smaller sized AVRs make the need to place initial larger sizes critical.

Reply 2: We agree with you that implanting a large prosthetic valve is important, but we think that it is not actually critical. Our results underline this concept: Of the 8 patients (15%) with small PMEs (19/21 mm), increased late gradients with the need for valve-in-valve TAVR were only seen in 2 patients. Only one additional patient had morphologic alterations of the PME with moderate hemodynamic impairment. The remaining 5 patients had increased AV gradients without progression and without morphologic alterations. An increased mean transprosthetic gradient of 20-25 mmHg was usually well tolerated.

Changes in the text: No changes.

Comment 3: Please include a detailed discussion of the valve degeneration data in the light of subsequent TAVR to address degeneration.

Reply 3: We agree with you and added this aspect to the discussion.

Changes in the text: We added to the discussion "SVD can now be managed with reasonable risks using valve-in-valve TAVR. However, the long-term durability of valve-in-valve TAVR remains largely unknown. Thus, the risk of open reoperation with known long-term durability of surgical bioprostheses still needs to be contemplated against valve-in-valve TAVR." (see **Page 10, Lines 232-235**).

Comment 4: The size of the aortic sinus and coronary height particularly may impact the decision of initial valve size choice and need for root enlargement to plan for subsequent TAVR. Do the authors have data on the sinus sizes and coronary height of the study population.

Reply 4: Selection of the adequate prosthesis's size was based on the manufacturer's aortic annulus sizers with respect to the coronary height, but unfortunately we don't have data on the sinus sizes and coronary height of the study population. See also Comment 1.

Changes in the text: No changes.

Comment 5: Were reoperations all open surgical procedures or TAVR?

Reply 5: All reoperations were TAVR.

Changes in the text: No changes.

Reviewer B

Comment 1: The hemodynamic advantages of the Manga Ease have been reported before and are known in the community. The data presented helps to underline the good performance of the prosthesis. Besides this, I am not sure what the learning points from the manuscript are?

Reply 1: Most studies reporting hemodynamic results of bioprosthetic valves are cross-sectional studies which only report the echocardiographic finding at discharge and/or last follow-up. Our study describes serial echocardiographic data of the PME. We observed, that patients frequently presented with an increased mean transprosthetic gradient during follow-up. Due to our study design, we were able to tract these patients and investigate the course of the gradient and their clinical status. Furthermore to our knowledge, there is no 10-year follow-up data of the PME available in the current literature.

Changes in the text: No changes.

Comment 2: Especially I do not realy understand the point that serial annual echocardiography changes the course of patients? As stated by the authors themselves, if there are no clinical symptoms and/or the patient is too fragile there will be no indication for intervention.

Reply 2: In the present investigation, the annual echocardiographic evaluation helps to accurately describe the performance of the PME. We disagree that regular echocardiographic check-up after implantation of a bioprosthetic valve does not affect the clinical course of the patients: without regular echocardiographic check-up, the development of SVD and its worsening might be detected too late when the heart has already taken damage or severe symptoms are present. Indeed, based on the annual echocardiographic examinations six patients underwent reintervention in time with good clinical outcome.

Changes in the text: No changes.

Comment 3: More interesting (from my view) would be data on patients at risk for SVD i.e for patients with patient-prosthesis mismatch. You mentioned moderate and severe PPM. What happened to these patients? Was there earlier SVD?

Reply 3: We agree that this is an interesting point. We analyzed the results based on the PPM. For patients with moderate and severe PPM at discharge, the 10-year outcome was as following: survival = 80.4±10.4% and 50±20.4%; cumulative incidence of SVD Stage 3 =

19±9.8% and 17±20.4%; cumulative incidence of BVF = 19±9.7% and 33±19.2%. In our cohort survival at 10 years after PME implantation for patients with moderate PPM was 80% associated with a 19%-incidence of both, SVD Stage 3 and BVF. Severe PPM was associated with worse 10-year survival (50%) and increased incidence of BVF (33%). The groups no PPM (n=33), moderate PPM (n=18), severe PPM (n=6) were relatively small for a meaningful statistical comparison and a detailed discussion in the manuscript. Nevertheless, we do not want to withhold these results from the reader. Therefore, we included a detailed table in the supplementary appendix.

Changes in the text:

We added to the section Results: "A detailed description of survival, BVF, SVD and NSVD depending on the presence of PPM at discharge is attached in the Supplementary Appendix." (see **Page 8, Lines 164-166**).

We added to the section Limitations: "Due to the small size of the groups, a statistical comparison of patients with none, moderate and severe PPM was not feasible and regression analysis for risk factors for SVD was not performed (see **Page 12, Lines 272-275**).

Reviewer C

We thank the reviewer for his/her thoughtful comments.

Comment 1: The title is misleading. The authors write about evaluating SVD in biological valves, but they only evaluated Perimount Magna Ease. The title should be changed.

Reply 1: We agree.

Changes in the text:

We altered the title to: "Serial echocardiographic evaluation of the Perimount Magna Ease prosthesis". (see **Page 1, Line 1**).

Comment 2: Analysis of concomitant interventions The authors state that 13 cases also underwent aortic surgery. I wonder why in the case of surgery on the ascending aorta (I assume there was a comorbid aortic aneurysm) no biological aortic prostheses were used with a biological valve or mechanical prostheses? Additionally, if there was a coexisting aortic aneurysm, this information should be included in Table 1.

Reply 2: In the 8 patients (13%) additional aortic procedures were performed: in 2 patients supracoronary replacement of the ascending aorta and in 6 patients reduction plasty of the ascending aorta (plication of the ascending aorta with two corresponding felt strips). Six

patients had a preoperatively diagnosed aneurysm, and 2 patients showed intraoperatively a pathologic enlarged ascending aorta. No patient had an aneurysm of the aortic sinus/root. Therefore, replacement of the ascending aorta was only performed supracoronary and no composite conduit (prosthetic valve + aortic prosthesis) was used. Meanwhile, due to unsatisfying results we have abandoned the technique of aortic reduction plasty. As the focus of the manuscript is different, only certain operative details are described in the manuscript.

Changes in the text:

Number of the patients with ascending aortic aneurysm were included in Table 1 (see **Page 18**). In Table 2, we changed "Replacement of the ascending aorta" to "Supracoronary ascending aortic replacement". (see **Page 20**)

Comment 3: Was aortic root enlargment performed in patients with small aortic root?

Reply 3: No, see also Reviewer A: Comment 1.

Changes in the text: We added to the discussion "In young patients and patients with small aortic annulus who are at risk for future reintervention due to SVD, aortic root enlargement in combination with SAVR facilitating the implantation of a larger prosthetic valve should be kept in mind. In the meta-analysis by Yu et al. aortic root enlargement was found to be a safe adjunct to SAVR resulting in larger implanted prosthetic valves and less PPM possibly improving future valve-in-valve TAVR outcomes (19). They could also show that addition of aortic root enlargement to SAVR does not increase early adverse events such as myocardial infarction, permanent pacemaker implantation, reoperation for bleeding, or stroke. However, aortic root enlargement increases the extent of the operation resulting in increased aortic cross-clamp time which was associated with increased late mortality (20). In the present study, none of the patients received aortic root enlargement." (see **Page 10, Lines 235, 236, Page 11, Lines 237-245**).

Comment 4: If there was no endocarditis, it should be present in Table.

Reply 4: Endocarditis is present in Table 1.

Changes in the text: No changes in the text.

Comment 5: EuroScore II or STS data are missing.

Reply 5: We agree with you and EuroScore II was calculated and added in Table 1

Changes in the text: EuroScore II was added in Table 1 (see **Page 19**).

Comment 6: The discussion is well written with most of the most commonly implanted valves on the market being comparable. However, I miss a description of the new generation of valves intended for implantation in young patients to avoid SVD. The new generation RESILIA ™ tissue aortic valve bioprosthesis showed excellent hemodynamic performance and safety results at one year follow-up. The prevalence of SVD was already present in detail at the one-year follow-up (Bartuś, Krzysztof, et al. "Primary safety and effectiveness feasibility study after surgical aortic valve replacement with a new generation bioprosthesis: one year outcomes." Kardiologia Polska = Polish Heart Journal 76.3 (2018).) And also in mid-term outcomes (Bartus, Krzysztof, et al. "Final 5-year outcomes following aortic valve replacement with a RESILIA ™ tissue bioprosthesis." European Journal from Cardio-Thoracic Surgery 59.2 (2021) : 434-441.) In the modern era of cardiac surgery, it is very important to present these results, especially when the TAVI technique is used more frequently.

Reply 6: We agree.

Changes in the text:

We added in the discussion: “New generation heart valves made with tissue designed to reduce calcification, such as the RESILIA (bovine pericardial, Edwards Lifesciences, Irvine, CA, US) prosthesis, showed no SVD up to 5 years of implantation (17, 18). When comparing this valve to the PME, equal rates of SVD 5 years post implantation were seen, and the potential long-term advantage of the RESILIA prosthesis still needs to be proven.” (see **Page 10, Lines 227-231**).

Reviewer D

Comment 1: The major limitation of this manuscript is probably the sample size (N=58), which is remarkably lower than sample sizes in previous studies aimed at evaluating the durability of this and other bioprostheses. This remains a major limitation the Authors do not address or comment, since an adequate sample size is important to correctly evaluate these valve-related outcomes. The Authors should justify their choice, i.e. based on serial in-house yearly echocardiography examinations for all patients, or relatively recent introduction of this bioprosthesis.

Reply 1: We agree and altered the limitations. We are a cardiovascular surgical department with limited capacity for pre-, postoperative and selected follow-up echocardiographic examinations.

Changes in the text:

We changed the limitations: “The present single-center study was limited by its non-randomized and retrospective design. Furthermore, the study was limited by the relatively small number of patients and the available serial echocardiographic evaluation over the course of 10 years. Standardized follow-up protocol was performed in the initial patients, in whom a PME was implanted. Due to the small size of the groups, a statistical comparison of patients with none, moderate and severe PPM was not feasible and regression analysis for risk factors for SVD was not performed.” (see **Page 12, Lines 269-275**).

Comment 2: It seems that the rates of freedom from SVD were calculated according to the actuarial (Kaplan Meier) method only. The little number of patients and events prevents from providing adequate competing risks analysis and calculation of corresponding freedom rates, which is an additional limitation.

Reply 2: Competitive risk analysis (eg. cumulative incidence rates of reoperations vs. death without reoperation) have very similar requirement to the number of patients as the Kaplan Meier method. In both methods including fewer patients results in larger confidence intervals. We have used the competitive risk analysis to describe the cumulative incidence of SVD, BVF, and NSVD. Survival was calculated with the Kaplan Meier method. The confidence intervals are depicted as shaded areas in the corresponding curves.

Changes in the text:

We clarified in the section Methods: “SVD, NSVD, and BVF were analyzed with a competitive risk analysis calculating the cumulative incidence.” (see **Page 6, Lines 121, 122**).

Comment 3: In order to facilitate comparison with previous series, please present freedom from SVD not only as cumulative incidence rates, but also as % freedom rates at 5 and 10 years.

Reply 3: We agree.

Changes in the text:

We added to the section Results: “Freedom from any SVD at 5 and 10 years was 100±0% and 68.9±7.3%, respectively.” (see **Page 8, Lines 171, 172**). “Freedom from SVD Stage 3 at 5 and 10 years was 100±0% and 82.8±6.1%, respectively.” (see **Page 8, Lines 175, 176**).

Comment 4: Remarkably, all 6 patients requiring reintervention for SVD received a valve-in-valve TAVI. Please clarify whether all of them were considered to be at high or prohibitive reoperative risk.

Reply 4: We agree.

Changes in the text:

We added to the section Results: "EuroSCORE II at time of reintervention was 4.2±1.5%." (see **Page 7, Line 157**).

Comment 5: Please specify the anticoagulation/antiplatelet therapy which was given after surgery to the recipients of these bioprostheses. Also, the Authors indicate that during follow-up some patients showed increased average transvalvular gradients, with reduction on subsequent echocardiography exams. Was this potentially associated with valve thrombosis? Were these patients treated with anticoagulants before decrease in gradients?

Reply 5: Postoperative anticoagulation regime was already described as following: "After operative treatment, all patients were anticoagulated with phenprocoumon for 3 months. Anticoagulation was continued if there were other indications for permanent use." Despite measurement of increased mean AV gradients the morphology of the prosthetic valve leaflets was normal in transthoracic echocardiography. We are aware that recent publication have shown that formation of microthrombosis might lead to elevated AV gradients without visible changes of the prosthesis in echocardiographic evaluations (Basra SS et al., Ann Thorac Surg. 2018, 106:1716-1725). However, these findings are relatively new and thus we have not applied anticoagulation therapy in patients with increased AV gradients without morphologic alterations of the PME.

Changes in the text: "Also, recent findings have shown that microthrombosis of prosthetic valve leaflets detected during four-dimensional computed tomography might be a cause of temporary elevated mean pressure gradients (23)." (see **Page 12, Lines 265-267**).

Comment 6: The Introduction can be shortened, as definition of valve-related adverse events can be moved to the Methods section.

Reply 6: We agree. Actually, we found that all descriptions and definitions of NSVD, SVD, and BVF provided in the section Introduction were described in the section Methods already. Thus, we decided to shorten the section Introduction without moving the descriptive part of NSVD, SVD, and BVF to the section Methods.

Changes in the text: The paragraph on the section NSVD, SVD, and BVF was deleted in the section Introduction and adapted in the section Methods. "Evaluation of non-structural valve

dysfunction (NSVD), SVD, and bioprosthetic valve failure (BVF) was done according to the standardized definitions of structural deterioration and valve failure by Capodanno et al. (6) (Fig. 1). NSVD is characterized by a morphologic not altered prosthetic valve but with impaired function due to leaflet thrombosis, endocarditis, intra- or para-prosthetic regurgitation or PPM. SVD is characterized by intrinsic permanent changes of the prosthetic valve either without hemodynamic impairment (morphologic=Stage 1) or with hemodynamic impairment (moderate=Stage 2; severe=Stage 3) (Fig. 1). If the patient's clinical condition is impaired by SVD Stage 3 or NSVD resulting in valve-related death or repeat intervention (valve-in-valve TAVR, paravalvular leak closure or SAVR) the criteria for BVF are met (Fig. 1)." (see **Page 5, Lines 103-112**).

Comment 7: Pericardial bioprostheses have been initially suggested to potentially provide a better durability than porcine bioprostheses. Based on the current data and comparison with the literature, it seems that the performance of this recent valve with respect to SVD is not different than porcine valves. Can the Authors comment on this point?

Reply 7: We think to make a qualified comment on this topic, it is absolutely mandatory to do a proper literature review in terms of a meta-analysis or systematic review. Furthermore, this is beyond the scope of this investigation. Nevertheless, to provide the interested reader with a little more detail on this topic, we added to all bioprosthetic valves mentioned in the discussion, if it was porcine or bovine pericardial.

Changes in the text: We added to the discussion: "Hancock II prosthesis (porcine, Medtronic, Minneapolis, MN, US)" (see **Page 10, Line 212**); "Sorin Mitroflow (bovine pericardial, Sorin Group Canada Inc. Mitroflow Division, BC, Can)" (see **Page 10, Lines 216, 217**); "Perimount prosthesis (bovine pericardial)" (see **Page 10, Line 222**); "RESILIA (bovine pericardial, Edwards Lifesciences, Irvine, CA, US)" (see **Page 10, Line 228**); "Medical Trifecta prosthesis (bovine pericardial, St Jude Medical, Inc., St Paul, MN, USA)" (see **Page 11, Lines 250, 251**).

Comment 8: The Authors should provide the average delay and delay range to occurrence of SVD. As well, the title should be probably reformulated as the article does not investigate the 'course' of SVD: too few events are available to longitudinally evaluate the evolution of SVD from stage 1 through stage 3.

Reply 8: We agree. As the study was ended after 10 years, it is not reasonable to provide a maximum range.

Changes in the text: We added to the section Results: "the average time was 8.2±1.9% years." (see **Page 8, Line 173**). We changed the title to "Serial echocardiographic evaluation of the Perimount Magna Ease prosthesis" (see **Page 1, Line 1**).