Peer Review File

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Reviewer A

The authors describe their experience in the treatment of patients with combined aortic and mitral regurgitation with TAVR. Although the experience reported is interesting, there are some issues that should be addressed:

1. The concept that a functional mitral regurgitation can improve after TAVR in aortic stenosis is well established. I think that this concept should be stated in the text with the proper citations because it supports the idea that the resolution of one valvulopathy can lead to an improvement of the other (even if in the present paper the patients treated are patients with aortic regurgitation)

Reply: Thanks for the comment. We have added citations and text as advised (Page 3, line 10).

Changes in text:

… Notably, concomitant mitral regurgitation is more likely to happen in patients with aortic valve dysfunction. Combined aortic and mitral value dysfunction raises the challenge to either surgical or transcatheter treatment. Studies showed that mitral regurgitation would be improved in 40~100% AS patients who receiving surgical aortic valve replacement (SAVR), however, the improvement was less (12~80%) in those who receiving TAVR (7). Real-world data of applying TAVR for aortic regurgitation is increasing, which supports TAVR for appropriate AR patients (8). While mitral valve regurgitation is also common in AR patients, whether TAVR would be efficacy for combined aortic and mitral regurgitation remains unclear…

2. On line 5 the authors state that they excluded patients having serious complications after TAVR. This should be explained better (have this patient had complications independent from the presence of concomitant MR? In this case this data could affect the safety of the combined procedure).

Reply: Thanks for the comments. We have addressed the exclusion criteria for serious complications or failure of TAVR, not after TAVR, which included changing TAVR to surgical valve replacement or death during operation. (Page 4, line 17). All these exclusions had no relationship with concomitant MR, and would not affect the final conclusions. We did include one patient who received aortic stenting during operation and recovered well after TAVR (Page 5 line 26).

3. On page 7 the authors state their criteria for the exclusion of transfemoral route in patients with AR. They should explain them thoroughly considering that nowadays transapical route has been abandoned in most centers.

Reply: Thanks for the comments. It's true that transapical route is less performed in some centers. However, different from AS, AR resulted in severe dilation of aortic ring more common. The failure of transfemoral route increased when diameter of aortic ring was more than 27mm. More details we had addressed in text (Page 7 line 22). Therefore, whether transapical or transfemoral route should be applied was based on the image data and experiences. We also added explanation as advised (Page7 line 17, 27).

Changes in text:

In our experience, AR resulted in severe dilation of aortic ring and had higher chances of failure due to unable to stabilize the prothesis. Therefore, …

… Transapical route could be applied for those who were not suitable for transfemoral route as there were three stabilization arms in prothesis for transapical route. We included TAVR of both transfemoral and transapical routes in our study, and no differences were observed between them.

4. The conclusions should be changed: TAVR procedure is feasible in this setting of combined disease and can lead to an improvement of the functional MR. In patients with significant residual MR, moreover, a staged procedure on the mitral valve could be speculated.

Reply: Thanks for the comments. We have changed text as advised (Page 8 line 19).

Change in text: … and can lead to an improvement of MR. In patients with significant residual MR, moreover, a staged procedure on the mitral valve could be speculated.

More than as a paper, this work might be evaluated as a case series. The overall quality of the manuscript should be improved to be considered for publication in this journal.

Reviewer B

This reviewer acknowledges the efforts of the authors detailing their experience using a self-expanding TAVR prosthesis for severe AR in patients with moderate or severe functional MR. As noted, coexistent valve disease is considered a relative contraindication; additionally, concerns with anchoring limit broad applicability of TAVR in this population. This reviewer asks the authors to consider the following comments to strengthen this well written manuscript:

1. Please clarify the decision-making process to select patients for TAVR or surgical valve replacement. If there is a comparable surgical group undergoing aortic valve replacement without co-existent mitral intervention, consider adding them as a comparison cohort.

Reply: Thanks for the comments. We added the text as advised (Page 4 line 11). It would be very difficult to include comparable surgical group in our study as most patients with combined valvular disease received mitral valve replacement or valvoplasty when having SAVR. However, we did find some results from Nombela-Franco's review following reviewer's comments. In the review, either SAVR or TAVR would result in a reduction in MR in most patients, regardless of persistence of MR in some patients (Nombela-Franco L, Ribeiro HB, Urena M, et al. Significant mitral regurgitation left untreated at the time of aortic valve replacement: a comprehensive review of a frequent entity in the transcatheter aortic valve replacement era. J Am Coll Cardiol. 2014;63(24):2643-2658. doi: 10.1016/j.jacc.2014.02.573.).

We will also include these patients with SAVR in the further observation.

Changes in text:

…Patients with following conditions were suggested for TAVR: (1) severe aortic regurgitation confirmed by echocardiogram; (2) NYHA functional class III or IV; (3) surgical contraindications with society of thoracic surgeons score ≥ 8; (4) desire to receive TAVR. The inclusion criteria for study were as…

2. The negative remodeling of the left ventricle is notable with changes in the mitral annular diameter, even at one month post TAVR implant. Please add comparison of left ventricular ejection fraction, pre-and post-intervention.

Reply: Thanks for the comments. We did compare both diameter and ejection fraction (EF) pre- and post- intervention, however, no statistical significances were observed. The results were added as advised (Page 5 line 33). Importantly, we further compared the LVEF post-intervention with that of 1-month follow-up, the LVEF significantly increased (44.6%±9.3% post-operation vs. 50.0%±9.4% 1-month follow-up, P=0.022). We added this result and discussion in the text (Page 2 line 22, Page 6 line 8, Page 7 line 6).

Changes in the text:

… During the 1-month follow-up, the mean left ventricular ejection fraction was significantly improved (50.0%±9.4% vs. 44.6%±9.3% at admission, P=0.022).

… No significant improvements of EF were seen within 24 hours post-operation (44.6% ± 9.3% post-operation vs 46.4%±14.3% at admission, P=0.529) …

… LVEF increased by nearly 5% (44.6%±9.3% post-operation vs. 50.0%±9.4% 1-month follow-up, P=0.022).

…. Though the LVEF slightly decreased post-operation, cardiac function was significantly improved as LVEF increased at 1-month follow-up. There were no statistic improvements of LVEF between at admission and follow-up, which may be related to the small sample size and the overestimation of EF values due to the presence of MR before TAVR.

3. The primary concern with TAVR in primary Aortic regurgitation is anchoring. Other than aortic valve sizing is their other findings the team looks for to improve the likelihood of anchoring as part of patient selection?

Reply: The review addressed the very important point for TAVR in AR, especially for transfemoral route. There were two factors we would carefully evaluate in AR patients for TAVR: aortic annulus sizing and ascending aorta sizing. The aortic annulus and ascending aorta provided anchoring for self-expanding TAVR. When the diameter of aortic annulus exceeded 27mm and that of ascending aorta exceeded 40mm, we considered high risk of failure for transfemoral route. However, TAVR of transapical route provided additional anchoring by inserting three arms into sinus, and would be efficient for those who with large aortic valve ring.

4. Please include changes in mitral annular area / shape in addition to the aforementioned diameter.

Reply: Thanks for the comments. We agree that more data would provide better understanding when comparing the improvement, however, as mitral annular area/shape is less evaluated for MR, most of the data were not collected in this study originally. It's almost impossible to include the changes as advised. We added text to address that more details should be included in future study (Page 6 line33).

Changes in text:

… MR was significantly improved in our study as mitral annular diameter reduced. However, more data, such as in mitral annular area/shape, may further illustrate the details of improvement.

Reviewer C

1. Please check below three abbreviations in the main text. All abbreviated terms should be full when they first appear.

12 suggested for TAVR: (1) severe aortic regurgitation confirmed by echocardiogram; (2)
13 NYHA functional class III or IV; (3) surgical contraindications with society of thoracic
14 surgeons score ≥ 8; (4) desire to receive TAVR. The inclusion criteria for study were as

Left heart was significantly retrieved after TAVR as there was an average reduction of about 7mm in the LVEDD, along with the mitral annular diameter reduced nearly 5 mm after TAVR. No significant improvements of EF were seen within 24 hours post-

Reply1: Thanks for the comment. We have added citations and text as advised (Page 4, line 14; Page 5, line 34).

Changes in text:

Page 4, line 14:(1) severe aortic regurgitation confirmed by echocardiogram; (2) New York Heart Association (NYHA) functional class III or IV;

Page 5, line 34: Left heart was significantly retrieved after TAVR as there was an average reduction of about 7mm in the left ventricular end-diastolic diameter (LVEDD),

2. The main text should be structured with Introduction, Methods, Results, Discussion, and Conclusions. Please add **#Conclusions** section.

Reply2: Thanks for the comment. We have added citations and text as advised (Page 8, line 30-33).

Changes in text:

#Conclusions

TAVR is effective and feasible for high-risk patients with combined aortic and mitral regurgitation.

3. Please unify the Time span in the abstract and main text.

combined aortic and mitral regurgitation who were treated with TAVR at center of structural heart disease, Zhongnan Hospital of Wuhan Univeristy from December 2021 to November 2022 were retrospectively analyzed. Echocardiographic parameters of

Patients with severe aortic regurgitation (AR) and moderate/severe mitral regurgitation (MR) diagnosed at the Zhongnan Hospital of Wuhan University and treated with TAVR from January 2022 to November 2022 were enrolled in this

Reply3: Thanks for the comment. We have added citations and text as advised (Page 4, line 11).

Changes in text:

Patients with severe aortic regurgitation (AR) and moderate/severe mitral regurgitation (MR) diagnosed at the Zhongnan Hospital of Wuhan University and treated with TAVR from December 2021 to November 2022 were

4. Table 1-2:

1) Please indicate how the data are presented in Tables 1-2 footnotes. For example, Data are presented as No. (%) or mean ± standard deviation.

2) Please indicate the full name of "NT-Pro BNP", "RJA/LAA" in Table 2 footnote.

Reply4 1): Thanks for the comment. We have added text as advised (Page 13, line 5 and line 13).

Changes in text:

Page 13, line 5: Data are presented as No. (%) or mean ± standard deviation.

Page 13, line 13: Data are presented as mean ± standard deviation.

Reply4 2): We have added citations and text as advised (Page 13, line 1-4).

Changes in text:

STS, Society of Thoracic Surgeons; ALT, alanine aminotransferase; TBIL, total bilirubin; HGB, hemoglobin; NT-ProBNP, N-terminal prohormone of brain natriuretic peptide; AAo, ascending aorta; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; RJA, regurgitant jet area; LAA, left atrial area.