Author’s response to reviews

Title: Mid-term effect of balloon aortic valvuloplasty on mitral regurgitation in aortic stenosis

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Author’s response to reviews:

Response to Reviewer #1:

The authors are thankful to this reviewer for his or her thoughtful and constructive comments. This individual clearly has a high level of expertise and experience in this topic, and his or her insight for improving this manuscript is greatly appreciated.
1. I felt uncomfortable to see the sentences "Moreover, the Awaji Medical Center is not currently accredited for TAVR; thus, &gt;40 BAVs are performed annually at our center, which may have introduced some bias in the indications for BAV for patients with severe AS." in the limitations section. I am not sure whether it is a reasonable practice not to refer patients for TAVR just because the authors' hospital is not accredited for TAVR. I would like to ask the authors to provide the number of patients who had BAV due to the bias of Awaji Medical Center being not accredited for TAVR.

Thank you for your comment, and we agree with your query. We actually think that the treatment strategy for elderly AS patients are different between TAVR and non-TAVR institutions, and it is often difficult to transfer those patients for other appreciate hospitals. Our patients who were cardiogenic shock or acute decompensated heart failure or required non-cardiac surgery were good indication for BAV, otherwise elective cases (87/140, 62.1%) may perform primary TAVR in the hospital accredited for TAVR. In our opinion, there is ethical issue when doctors in the TAVR hospital do not perform TAVR for the severe AS patients appropriately indicated for TAVR. However, there is no ethical problem when doctors in the non-TAVR hospital perform BAV for severe AS patients indicated for TAVR. Previous study showed that the prevalence of severe AS in the elderly (&gt;75 years of age) was 3.4% (J Am Coll Cardiol. 2013 Sep 10;62(11):1002-12.). In Awaji island, there were 17097 elderly (&gt;75 years of age) at 2015, and then severe AS in Awaji island was estimated to 580 patients. Our hospital, as local base hospital, have to care for most of them. Though the population aging rate becomes higher in rural area than that in urban city, most of TAVR hospitals are really in urban city. In the present day, we cannot eliminate regional difference of healthcare between urban city and rural area, or among countries. In addition, elderly patients subject to such regional disparities.

Thus, the following sentence has been added to the Study Limitations.

Added to Page 12: “Our patients who were cardiogenic shock, acute decompensated heart failure or required non-cardiac surgery were good indication for BAV, otherwise Although elective cases in this study such as cardiogenic shock, acute decompensated HF, or immediately required non-cardiac surgery (62.1%) may undergo primary TAVR in the hospital accredited for TAVR, such patients were good indication for BAV as well.”.

2. According to the data provided, the mortality rate even within 3 months after BAV is about 22.8% (32/140). Therefore, I want to make sure that BAV is not a reasonable treatment option for severe AS in elderly patients, especially even in biased medical circumstances.

Thank you for your comment. In our data, 32 patients (22.8%) were died within 3 months after BAV. Cardiovascular death accounted for 7 cases (heart failure 4, thoracic aortic aneurysm rupture 1, rebleeding at puncture site 1, cerebral infarction 1), and non-cardiovascular death accounted for 25 cases (pneumonia 11, cancer 2, gastrointestinal hemorrhage 1, acute kidney injury 1, ANCA-associated vasculitis 1, surgical death 1, senile deterioration 3, unknown or unclassified 5). Because the number of heart failure death was small, we think that the treatment strategy, TAVR or BAV, have an insignificant effect on the mortality rate within 3 months after BAV.

We investigated 1-year mortality after BAV (Circulation reports 2020, in press). In this data, of 127 included patients, 41 (32.3%) died within 1 year after BAV, eight of which (19.5% of all-
cause deaths) were cardiac deaths. Higher grade of clinical frailty scale and STS score significantly correlated with 1-year mortality. Besides cardiac death was few, the parameters of AS severity both pre and post BAV had no relation to death within one year. From Japanese TAVR registry investigation (Shimura et al. Circulation 2017; 135: 2013-2024.), severe frail was also an independent predictor of 1-year mortality. We think the mortality rate of high aged AS patients were strongly associated with the indication of procedures. Therefore, the following sentence has been added to the part of Clinical implications.

Added to Page 12: “Moreover, the mortality rate even within 3 months after BAV was as high as 22.8% in this study, but most of them were non-cardiac death (78%).”.

3. Despite the ethical issue, this rare data is worth publishing. Thank you for your comment. In our region absented from TAVR there are many patients who were not indicated to SAVR but was not able to transfer to other TAVR institutions. We think many doctors and hospitals were faced with the same situation as us over the whole world. In this TAVR era, the data followed only BAV is very rare. In addition, we find better clinical efficacy and usability of BAV compared with the recent recognitions. Thus, we will advertise BAV clinical data and efficient use of it.

4. I would like to ask the authors to provide the changing percentage of MR severity as well as MR jet area (average +/- SD) in Figure 3.
Thank you for your important comment. We have changed Figure 3 to box plot with the view of easily visualizing the changing MR severity as your suggestion.
Compared with baseline the MR jet area at 1 month after BAV was 53.4 % (31.8 - 97.2 %) and at 3 months after BAV was 39.6 % (17.9 – 66.5 %). The changing of MR parameter was important, thus we have added the follow sentence.
Added to Page8; “In the MR group, the MR jet area at baseline was 6.3 cm2(4.5-9.7 cm2), and which gradually decreased at 1 month (3.5 cm2, 1.5-7.4 cm2) and at 3 months (2.1 cm2,1.1-6.0 cm2) after BAV.”

5. I would like to ask the authors to provide the box plot for MR jet area in each categories of Carpentier's classification. And also I would like to know how many type IIIa MR (rheumatic) were included in 15 of non-improved MR patients in MR group.
Thank you for your comment. As you pointed out, we have changed Figure 4 to box plot.
In 15 patients persisted significant MR at 3 months, 9 patients improved MR compared with baseline but remained significant MR (5 in Type I, 1 in Type II, 2 in Type IIIa, 1 in Type IIIb). And then, 6 patients worsened MR compared with baseline MR jet area (2 in Type I, 1 in Type II, 2 in Type IIIa, 1 in Type IIIb). Type I and IIIa were tended to remain significant MR, but there was no significant difference among each etiology groups. Thus, the following sentences have been added the part of Results.
Added to Page 8; “In 40 patients of the MR group, 25 patients (62.5%) improved MR jet area &lt; 4.0cm2 and 9 patients (22.5%) improved but remained significant MR, and 6 patients (15.0%) worsened MR compared with baseline. Categorized by MR etiology, persisted significant MR was showed 7/16 (43.8%) in Type I, 2/5 (40%) in Type II, 4/10 (40%) in Type IIIa, and 2/9 (22.2%) in Type IIIb. Though Type IIIb were tended to achieve much more reduction of MR, there was no significant difference among each etiology groups.”
6. Contrary to the authors' comments that MR tended to improve after BAV regardless of the etiology of MR in the MR group (with the improvement being significant for patients Type I, II and IIIb MR), Figure 4 showed us that Type II (organic MR such as prolapse, flail) had worst outcome at 3 months after BAV. The authors may want to comment on this issue.

Thank you for your important comment. As shown in Figure 4, the MR jet area was worst in Type II, but the median value of MR jet area reduced at 1 and 3 months after BAV in each etiology groups. Though some patients in Type II and Type IIIa had become worse in 3 months after BAV, the jet area was tended to reduce overall in MR group. To discuss about MR etiology, we have added to the following sentences.

Add to Page 11-12; “Differences among the etiology of MR. In this study, the reduction of LV cavity was the predictor of MR improvement. The effect for Type I and IIIb were recognizable, but Type II and IIIa which were leaflet issues were unclear. Though we could not find the statistically difference among the MR etiology in this small number study, it seems to be tendency of poor response in Type II and IIIa (Figure 4). On the other hand, even in Type II and IIIa cases showed significant decreasing of the MR severity at 1 month and 3 months after BAV. This finding can bring great clinical worth for too sick elderly patients with AS and MR because BAV is less invasive, easy-to-use and low cost treatment.”

7. I would like to ask the authors to provide the baseline parameters to predict significant MR at 1 months after BAV because change between baseline and 1-month after BAV is practically not useful to identify patients with severe AS for whom BAV could be of benefit to decrease MR.

Thank you for your comment, and we agree with your suggestion. In the MR group, LVEDD, LVEDS, MR jet area, mitral annular dimension at baseline were associated with the significant MR (MR jet area > 4cm2) at 1 month. On multivariate logistic regression analysis, larger LVEDD at baseline was an independent predictor of persisting significant MR at 1 month after BAV.

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR</th>
<th>95%CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDD, mm</td>
<td>1.31</td>
<td>1.098-1.567</td>
<td>0.003</td>
</tr>
<tr>
<td>LVEDS, mm</td>
<td>1.12</td>
<td>1.008-1.253</td>
<td>0.035</td>
</tr>
<tr>
<td>MR jet area, cm2</td>
<td>1.297</td>
<td>1.016-1.657</td>
<td>0.037</td>
</tr>
<tr>
<td>Mitral annular dimension</td>
<td>1.171</td>
<td>1.010-1.357</td>
<td>0.036</td>
</tr>
</tbody>
</table>

In the viewpoint of MR reduction at 3 months after BAV, the case with larger LV dimension at baseline and reduction of LV cavity and MR severity at 1 month is best responder. The main mechanism of MR reduction after BAV is considered that the reduction afterload by BAV introduce negative remodeling of LV and improvement of functional MR. The effect may bring not only to Type II but also other types of MR.

In our data, LVEDD at baseline and delta LVESD were significantly correlated. Thus, any baseline parameters including LVEDD was not significant predictor in MR at 3 months. Figure 3 showed gradual reduction of MR thorough 1 month and 3 months follow-up. And we think the MR severity at 3 months is more important in clinical setting than at 1 month. So, we want to discuss the changes of MR severity at 3 months after BAV.
Response to Reviewer #2:

The authors are thankful to this reviewer for his or her thoughtful and constructive comments. This individual clearly has a high level of expertise and experience in this topic, and his or her insight for improving this manuscript is greatly appreciated.

Major aspects

1. P2, L15-17: Result in Abstract, "The prevalence of NYHA class III or IV and BNP level also decreased at 1 and 3 months after BAV in the MR group but not in the non-MR group."
   This is not correct. The authors showed the NYHA class was improved in non-MR group as well in Figure 2.
   Thank you for your important comment. As you pointed out, we revised the following sentence in abstract.
   Add to Page 2; “The prevalence of New York Heart Association functional class III or IV decreased at 1 month and 3 months after BAV in both groups.”

2. Figure 4
   The authors did not show the actual number and dispersion of MR jet area in each etiology. Show the numbers or change the figure to box plot.
   Thank you for your comment, we have changed Figure 4 to box plot (Please see the response to Reviewer #1 comments ).

3. P8, L20: "significant MR persisted in 15 patients"
   How many patients were there whose MR degree did not improve?
   Thank you for your important comment. In 15 patients persisted significant MR at 3 months, 9 patients improved MR compared with baseline but remained significant MR (5 in Type I, 1 in Type II, 2 in Type IIIa, 1 in Type IIIb). And then, 6 patients worsened MR compared with baseline MR jet area (2 in Type I, 1 in Type II, 2 in Type IIIa, 1 in Type IIIb). Type I and IIIa were tended to remain significant MR, but there was no significant difference among each etiology groups. Therefore, the following sentences have been added to the Results.
   Added to Page 8-9; “In 40 patients of the MR group, 25 patients (62.5%) improved MR jet area &lt; 4.0cm2 and 9 patients (22.5%) improved but remained significant MR, and 6 patients (15.0%) worsened MR compared with baseline. Categorized by MR etiology, persisted significant MR was showed 7/16 (43.8%) in Type I, 2/5 (40%) in Type II, 4/10 (40%) in Type IIIa, and 2/9 (22.2%) in Type IIIb. Though Type IIIb were tended to achieve much more reduction of MR, there was no significant difference among each etiology groups.”

4. Table3
   I assume that mitral annular dimension, tenting height and tenting area will affect the remaining MR. How was the result of univariate analysis of these parameters? The change of these parameters will affect as well.
   Thank you for your very important comment. The changing of tenting area (r=0.388, p=0.013) and LVESD (r=0.480, p=0.002) were correlated with changing MR jet area at 3 months after
BAV. Moreover, LVESD and mitral annular dimension were strongly correlated at 3 months after BAV (r=0.463, p=0.003). Furthermore, changing of tenting area between baseline and 3 months after BAV was associated with persisting significant MR (OR=1.04, 95%CI=1.00-1.08, p=0.016). So, we consider that the decreasing mitral annular dimension, tenting height and tenting area will affect the same phenomenon about the reduction of LVESD. As same as you pointed, we also think mitral annular dimension, tenting height and tenting area affect the remaining MR, but multivariate analysis revealed only delta LVESD was independent predictor of remaining MR because of significant association between LV size and mitral valve.

5. P9, L21: Place of BAV in the TAVR era "we demonstrate that good clinical outcomes can be achieved at 1 and 3 months after BAV"
I have a feeling of wrongness on this expression of "good outcome". Thirty two of 140 patients (23%) were died in 3 months, and it is almost same as previous report. What is the ground of good outcome? The author's insistence can be applicable only for the patients who lived at 3 months after BAV.
P11, L17: Clinical Implications "to improve quality of life and prognosis"
Same as above, the authors did not investigate the prognosis in this study, they showed that the functional class of heart failure was improved after BAV.
Thank you for your comment, and we agree with your pointed out. The objective of this study was to investigate the effect of BAV on MR in patients with severe AS. We did not mean to clarify the prognosis after BAV. As you suggested, we have revised the sentence as follows.
Revised Page 12; “In this study, we demonstrate that good efficacy for severe AS with MR can be achieved at 1 and 3 months after BAV.”

Minor aspects

1. P2, L10: Result in Abstract, "BAV improved MR at 1 and 3 months after procedure"
We cannot know if only BAV improved MR. Change the representation.
Thank you for your comment. As your suggestion, we have revised the following sentence.
Revised Page 2; “Significant reduction of MR was observed in the MR group at 1 month and 3 months after procedure, with no improvement in patients in the non-MR group.”

2. P8, L3 "significantly improved at 1 and 2 months after BAV"
This must be 1 and 3 months after BAV.
Thank you for your pointed-out. The following sentence has been revised.
Revised Page 8; "significantly improved at 1 and 3 months after BAV"