

## Peer Review File

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### Response to Review A

The manuscript is very well written. The conclusion is limited by the small sample of 65 patients from single institutional dataset.

The major critique is the lack of controlling for preoperative differences when examining the outcomes. Would recommend multivariable analysis, such as logistic regression to eliminate the confounds.

Also, for the Tables title, please be more specific, e.g. Table 3 and table 4, what the time frame for short and midterm outcomes?

In conclusion, well written study with potential impactful findings. However, need to improve statistical methods for more definitive conclusions.

Reply: Thanks for your suggestion. This article was included the small sample of 65 patients. We need large cases to make multivariable analysis. We defined procedural outcomes as short outcomes and at least 1-year outcomes as midterm outcomes. To avoid ambiguity, we have changed short outcomes to procedural outcomes.

Changes in the text: see Page 7, line 206. Table 3

### Response to Review B

Major comments

Comment 1:

1. English and grammar should be improved, some examples:

- a. 11: perivalvular leakage and conduction block, , affecting the hemodynamic (delete one , )
- b. 113: valve.. (delete one .)
- c. 120: embolic disease, they were receive dual antiplatelet agents in the 3 months of the ("they were receive" is not grammatically correct)
- d. 121: postoperative period. They would also be presented with the prospect of permanent ... ("They would also be presented with the prospect of permanent" is not grammatically correct).
- e. 131: permanent pacemaker implantation.. (delete one .)
- f. 260 ... TAVs at procedural outcomes without severe paravalvular leakage. (This sentence should be: ... TAVs at procedural outcomes, without severe ...)
- g. 262 acceptable., (delete one ,)

Reply 1: Thanks for your suggestion. We removed these mistakes and changed some words.

Changes in the text: see Page 2, line 37. Page 5, line 150. Page 6, line 168. Page10, line299,301.

Comment 2: In the introduction the authors should use the novel Partner trials that are reflected in the references. They should also include the latest Partner 3.

a. Mack MJ, Leon MB, Thourani VH, et al; PARTNER 3 Investigators. Transcatheter Aortic-Valve Replacement in Low-Risk Patients at Five Years. N Engl J Med. 2023 Nov 23;389(21):1949-1960. doi: 10.1056/NEJMoa2307447..

Reply 2: Thanks for your suggestion. We have added references.

Changes in the text: Page13, line 406,407.

Comment 3: In the methods section the authors should define primary and secondary outcomes. Also they are missing inclusion and exclusion criteria, as well as time period.

Reply 3: Thanks for your suggestion. We have added this part.

Changes in the text: see Page 4, line 108-114.

Comment 4: In the abstract the authors state the relevance of perivalvular leakage in BAV. Meanwhile the authors fail to describe it on the procedural, early results section, they leave this important parameter in Table 3 and one sentence in discussion.

a. 258 .... In our study, the percentage of paravalvular leakage greater than mild was 6.90% in the BAVs and 5.56% in the TAVs at procedural outcomes...

b. This should be highlighted in abstracts and results.

Reply 4: Thanks very much for your suggestion. We have added this part in the procedural outcomes.

Changes in the text: see Page 7, line 206-209. Page 2, line57-58.

Comment 5: The authors also fail to address the risk of annulus rupture in post dilatation in calcified BAV.

Reply 5: Choosing the appropriate valves only reduces part of the risk of annulus rupture in post dilatation in calcified BAV. To solve these issues, this requires multiple factors of surgical methods and strategies. Ring rupture rarely occurs in our center.

Comment 6: The Discussion section should be changed: The authors must start by clearly presenting the answer to the goal of the study, then show how the answer is supported by the results. The first paragraph should summarize the study hypothesis, aims, and key findings. Subsequent paragraphs can be used to discuss any relevant published data

Reply 6: Thanks very much for your suggestion. We have added this part in the discussion.

Changes in the text: see Page 8, line 234-240.

Minor comments:

Comment 1: The title better describes the study in this way: Mid-term follow-up using "down-size" transcatheter aortic valve replacement to treat bicuspid aortic stenosis.

Reply 1: Thanks very much for your suggestion. This title referred to some other articles

Comment 2: In the abstract, on the Background section:

a. 12 we implemented different valve selection strategies to explore the safety and effectiveness of ...

Should not be described in this section, rather in methods.

Reply 2: Thanks very much for your suggestion. We added this part in methods.

Changes in the text: see Page 5, line 132.

Comment 3: Please do not use  $\pm$ , SD should be in parenthesis ().

Reply 3: Thanks very much for your suggestion. We deleted  $\pm$  and changed to mean (SD)

Changes in the text: see tables.

Comment 4: This should be in the methods section

150 double-blind peer review policy)) from January 2018 to December 2019, including 29

Reply 4: Thanks very much for your suggestion. We added this part in method.

Changes in the text: see Page4, line 108-115

Comment 5: When the authors state:

91 except in cases of peripheral femoral artery tortuosity, stenosis, or low height of the  
92 coronary opening.

Could they explain why is low height of the coronary opening an exclusion for transfemoral access? This should be an exclusion for all TAVI, so in this statement only artery tortuosity or stenosis should remain.

Reply 5: Thanks very much for your suggestion. In China, we have another TAVI system (J-valve system). It is a short frame valve with three graspers. J-valve was suited for low height of the coronary opening. We would choice J-valve for low height of the coronary opening patients.

Comment 6: 105.... Generally, the oversizing rate falls between 5-10%.

a. In this statement the authors should explain if this 5-10% refers to TAV and BAV both, or only one of the groups? If it's both, its recommended to show the difference in oversizing between both groups.

Reply 6: Thanks very much for your suggestion. This is our experience for the result of interventional valves. VenusA valves only consist of four models: 23, 26, 29, and 32 mm.

Comment 7: 168 operations did not result in any valve slippage, bleeding, or thoracotomy

conversion.

a. By thoracotomy you should mean sternotomy.

Reply 7: Thanks very much for your suggestion. Sternotomy may be more accurate word.

Changes in the text: see Page 7, line 205.

Comment 8: In the early results section, the authors state that 3 BAV died during the surgery. Please explain causes of death.

Reply 8: Thanks very much for your suggestion. The previous expression was not clear. Three patients died due to cardiac insufficiency, and one died due to pulmonary infection. They all died after TAVI. We added this part in the early outcomes.

Changes in the text: see Page 7, line 208-209.

Comment 9: Also, they state 4 deaths due to cardiac insufficiency and 1 pulmonary infection, on which group, BAV or TAV?

Reply 9: Thanks very much for your suggestion. They were BAVs.

### **Response to Review C**

This is a well-written, straightforward, and easy-to-read manuscript. Thank you for your contribution to share your clinical data to the readers. I agree with the body of the manuscript, but here are a few suggestions to improve your manuscript to be read easier by the readers.

Comment 1: Characteristics of the BAV. It is known that the raphe (if present) in BAV tends to calcify first that prevents the full opening of the interventional valve against the aortic wall. Clinical/imaging characteristics of the native stenotic valve would have helped the readers to imagine the scenario better.

Reply 1: Thanks very much for your suggestion. We plan to further study the imaging characteristics and fluid dynamics of BAVs.

Comment 2: TAVR or TAVI? These 2 terms are interchangeably used by many authors. But I suggest you stick with 1 term through out the manuscript. If TAVR was used in the title, please use TAVR in the body of the manuscript as well.

Reply 2: Thanks very much for your suggestion. We have changed TAVI to TAVR.

Comment 3: Favorable or Favourable? The words favourable and unfavorable were used in the same manuscript. Either is fine, but having consistency would improve the style of the manuscript.

Reply 3: Thanks very much for your suggestion. We have changed some words.

Changes in the text: see Page 11, line 332-333.

## Response to Review D

The paper “Transcatheter aortic valve replacement in the treatment of bicuspid aortic stenosis with “down-size” interventional valve: procedural and mid term follow up”, describes a single centre experience of 65 consecutive patients treated with transcatheter aortic valve implantation (TAVI) due to severe and symptomatic aortic stenosis in tricuspid (TAV, 36 cases) and bicuspid aortic valve (BAV, 29 cases). The Authors aim is to demonstrate the feasibility and efficacy of a “down-size” TAVI in BAV patients. It is an important issue, because TAVI in this setting still represents a challenge due to the peculiar anatomy and lack of consensus concerning the optimal method for multi-detector computed tomography (MDCT) scan sizing and prosthesis selection. Previous papers have tried to answer this issues (for example, Iannopollo G, et al. Supra-annular sizing of transcatheter aortic valve prostheses in raphe-type bicuspid aortic valve disease: the LIRA method. *Int J Cardiol* 2020;317:144–151. // Bicuspid Valve Sizing for Transcatheter Aortic Valve Implantation: The Missing Link. Giulia Costa, et al. *Front Cardiovasc Med.* 2021; 8: 770924. Published online 2022 Jan 27. doi: 10.3389/fcvm.2021.770924.)

The prosthesis down-size might make sense when TAVI anchoring, in BAV patients, occurs at the level of the raphe, in presence of high amount of calcium with a long raphe. In this way the new virtual basal ring is at the level of the raphe, instead of aortic annulus. The level we need to pay attention during MSCT analysis for sizing THV selection in BAV patients could be the raphe level.

However, the Authors did not explain their down-size method. They generally talk about a “relatively smaller size for BAVs” (pag 4, line 103) or using the “balloon’s shape” (pag 4, line 113) or “due to the structure and calcification of the two leaflets, a smaller valve was typically chosen” (pag 6, line 162), or they talk about “an oversizing rate between 5-10%” but no mention about the undersizing (pag 4, line 106). They reported an average annulus perimeter of 85.9 mm (mean annulus diameter of 24.5 mm) and implanted a prevalent of 26 mm and 23 mm VenusA devices. One can speculate, the undersized was simply obtained by [chart size annulus-1]. How to get at this choice? There is not a clear protocol helping with prosthetic sizing or a practical example in this experience. In another word, this paper can be difficult or impossible to reproduce.

Moreover, there is any mention about the bicuspid phenotype (type 0, Type I or II), or the anatomical characteristics in terms of amount of calcium and calcium distribution of 29 cases reported.

Introduction section:(pag 2, line 52) “TAVI is an innovative treatment for severe AS regardless the inherent surgical risk”instead of “[...] in high risk patents”: today TAVI is a treatment also for low risk patient, as reported in Discussion section (pag 9, line 274-282. Better to report it in Introduction section)

The description of VenusA valve (pag 7, line 199-208) should be better in Methods section. This paper is not a trial, as reported in pag 5, line 127 but a prospective observational study.

Reply: Thanks very much for your suggestion. We also choose the models based on the valve annulus and intraoperative balloon. If we can choose two different size valves, we tend to choose the smaller valves for BAVs, not only choose the small size valves for BAVs. This article was discovered through our later summarization of data. During our surgery, this experience was still relatively limited. In the later stage, we will summarize our experience based on large sample data. Perhaps AI may help us form a complete solution.

We also changed some words and paragraph.

Changes in the text: see Page 3, line 79-80. Page 5, line134-138.