Peer Review File

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Reviewer A

The authors present a small, single-center case series of patients with severe aortic stenosis treated with surgical aortic valve replacement with the rapid-deployment Edwards Intuity valve comparing outcomes of trileaflet vs bicuspid valves. In addition, they compared subgroups of bicuspid valves comparing Sievers 0 to Sievers 1 bicuspid valves. The report is comprehensive but suffers from all of the typical limitations of this type of observational study.

Comments:

1. The major problem with this report stems from the patient selection. Although your cohorts are similar based on baseline characteristics, you do not report any inclusion or exclusion criteria for patients to receive an Intuity valve. Please describe how patients were selected and who were not candidates for Intuity.

Reply:
Thank you for the valuable input. While I did mention the exclusion of patients with mechanical and conventional tissue valve implantation in the main text, I will enhance the clarity of the exclusion criteria in *Figure* 1. The choice between tissue and mechanical valves was made in consultation with the patient, taking into account their age and preferences. Moreover, I will elaborate on the indications for RD AVR. RD AVR was preferred for patients with aortic stenosis as the primary pathology, small aortic annulus (less than 21m on CT), severe aortic annulus calcification, concomitant cardiac surgery, or other factors indicating high surgical risk. Individuals presenting with aortic regurgitation as the primary condition or exhibiting severe calcification in the left ventricular outflow tract were not considered candidates for RD AVR. Surgeon preference also played a role in this decision. Hence, I will acknowledge the potential for selection bias in the discussion section.

Changes in the text:
see Page 6, line 109~111
“The choice between tissue and mechanical valves was made in consultation with the patient, taking into account their age and preferences.”

see Page 6, line 112~118

“RD AVR was preferred for patients with aortic stenosis as the primary pathology, small aortic annulus (less than 21m on computed tomography), severe aortic annulus calcification, concomitant cardiac surgery, or other factors indicating high surgical risk (14). Individuals presenting with aortic regurgitation as the primary condition or exhibiting severe calcification in the left ventricular outflow tract (LVOT) were not considered candidates for RD AVR. Surgeon preference also played a role in this decision.”

see Page 14, line 305~307

“Not being a prospective, randomized controlled clinical trial, there is a potential for selection bias in this study. When adopting a new procedure, the early experience involves some level of surgeon preference in patient selection.”

see Page 19, line 414~415

“14. Laufer G. The 10 commandments of rapid deployment Intuity valve implantation. Innovations (Phila). 2023;18:316-9.”

2. Following #1, this work would be much more powerful if it included ONLY patients who underwent AVR. You have a mix of pathology and concomitant procedures that make your findings less useful.

Reply:

Thank you for the insightful feedback. However, in the case of a bicuspid aortic valve, it is often associated with concurrent conditions such as aortic aneurysms. Moreover, patients requiring only aortic valve replacement nowadays are frequently discussed in multidisciplinary meetings, with a tendency toward deciding in favor of transcatheter aortic valve replacement. As you mentioned, the increasing prevalence of concomitant procedures reflects the reality, and it is appropriate to consider these practical aspects.

3. Following from #1, how many patients were intended to receive an Intuity, but the procedure was aborted, and the patient received a traditional surgical valve?

Reply:

In our early experience with RD AVR, there were no cases where an attempt to insert the Intuity valve resulted in conversion to a traditional tissue valve.

4. Due to the small number of patients, you cannot perform any meaningful matching, and all statistically significant findings could be due to chance, bias, and patient selection (since your cohorts are not controlled/randomized at baseline). Be very careful drawing any conclusions beyond "associations" as ALL of your data is nothing more than hypothesis generating.

Reply:
I fully agree with your perspective. We acknowledge that our research findings may lack robust statistical significance. If it were a multicenter study with a large dataset, it could have yielded greater statistical power. However, given that our study is rooted in the experience of a single institution with limited cases, we believe it remains of considerable interest to JTD readers. To strengthen the evidence, we understand the importance of amalgamating diverse types and levels of research. We believe these findings should be applicable even in smaller single-center settings. We find significance in sharing our experience of successfully conducting RD AVR in bicuspid cases (including Sievers type 0 bicuspid), even in less-experienced centers.

5. Following #3, with so few patients, would this work be better as a case series focusing on your implantation technique and learning curve?

Reply:
I appreciate your valuable input. Instead of detailing individual cases in a case series, I think that comparing surgical outcomes between tricuspid and bicuspid cases, even with a small sample size and statistically less significance, will capture the interest of readers. In clinical practice, many surgeons find it crucial to assess the differences in outcomes between tricuspid and bicuspid cases during RD AVR procedures.

6. Following #4, with only 14 bicuspid patients, further "subgroup" analysis is futile. You carefully selected 14 patients you believed would have a good result, completed the procedure, and had a pretty good result. It's just a small case series.

Reply:
I agree with your opinion. Nevertheless, the reason for conducting subgroup analysis is not to find additional statistical significance, but to separately present pre- and postoperative data for type 0 bicuspid patients and other bicuspid patients, aiming to demonstrate their distinct characteristics. Therefore, it was prepared as supplementary data because. In the case of Sievers type 0, there is still a lack of evidence for applying

RD AVR, and there are challenging aspects in the surgical technique. Additionally, since the prevalence of Sievers type 0 bicuspid is very low, and the case volume may be limited, even in small single centers with a low cardiac surgery volume, we wanted to show that RD AVR is feasible in type 0 bicuspid aortic valves.

Changes in the text: see Page 15, line 313~316
"The purpose of performing subgroup analysis is not to discover additional statistical significance but to present the pre- and postoperative data separately for type 0 bicuspid patients and other bicuspid patients, aiming to demonstrate their distinct characteristics."

7. Careful editing is needed in the abstract and throughout the manuscript. Please review the entire manuscript for errors. (Example: Abstract – none .., in "either" group)

Reply:
Thank you for the valuable input. I have reviewed, made necessary corrections, and incorporated them.

8. In general, try to be consistent in your presentation of data – A vs B and keep in that order throughout. You tend to flip back and forth and then present D, then C, which makes it very confusing. Try to make it easy for the reader to understand what you are telling them.

Reply:
Thank you for the helpful suggestion. To make it more straightforward, I have changed the designation of the Type 0 bicuspid patient group from 'D' to 'B0' and the other types of bicuspid patients from 'C' to 'B1'.

9. In the era of TAVR, 19-22 mm valves with mean gradients in the double digits are no longer acceptable. Why did these patients not receive root enlargements?

Reply:
I appreciate your insightful suggestion regarding the surgical approach. Aortic root enlargement, indeed, emerges as an important surgical alternative. The selection of the surgical technique is influenced by the surgeon's preferences and the collective experience of the center. Aortic root enlargement surgery comes with its drawbacks, including extended operative time, heightened bleeding risks, and potential postoperative arrhythmias. This procedure may present challenges for smaller centers with limited surgical volumes. Acknowledging the prevalence of numerous small centers in the real world, we believe that our institution's surgical outcomes bear clinical

significance, given these practical considerations. With the accumulation of experience in our center, we foresee a more frequent application of aortic root enlargement and plan to undertake further research in this domain.

9b. When implanting such small valves, there will be no (or minimal) options for a TAV-in-SAV when they fail. How did your heart team consider lifetime management?

Reply:
In our institution, the treatment plan for aortic stenosis patients is established through multidisciplinary discussions. After small prosthetic valve implantation, the possibility of valve-in-valve transcatheter aortic valve replacement is considered in advance before determining the surgical treatment.

10. In the abstract conclusions, avoid conclusions not supported by data – you cannot claim superiority in an observational study.
Truth: In a small, carefully selected cohort of patients with bicuspid aortic stenosis, RD AVR was "associated with" better postoperative hemodynamic outcomes …

Reply:
We wholeheartedly agree with your statement. We will make the necessary adjustments and incorporate them.

Changes in the text: see Page 3, line 58~61
"In this study, RD AVR was considered feasible in a small, carefully selected cohort of patients with aortic stenosis, even in BAV, including Sievers type 0, as observed from the standpoint of postoperative hemodynamic outcomes and the incidence of aortic regurgitation."

11. Line 53 – a decrease in procedural times – as compared to what?

Changes in the text: see Page 4, line 79~80
"when compared with conventional AVR"

12. Line 55-57 regarding superior hemodynamics needs a reference.

Changes in the text: see Page 4, line 81
"(2)"

13. Line 76 – please look up the definition of a “scoping review” and confirm what you have presented. This is a single-center, retrospective observational cohort study.

Reply:
We fully endorse your statement. We will implement the required modifications accordingly.

Changes in the text: see Page 5, line 100~
“single-center, retrospective observational cohort study”

14. Methods – Patient selection needs to be further defined.
-How was a patient selected for RA-AVR?
-Did they have a preop CT?
-Were there exclusion criteria?

Reply:
I appreciate your thoughtful question. I have addressed the exclusion of patients with mechanical and conventional tissue valve implantation in the main text. The decision between tissue and mechanical valves was made through discussions with patients, considering their age and preferences. Additionally, I will provide more details on the indications for RD AVR. RD AVR was favored for patients with aortic stenosis as the primary pathology, a small aortic annulus (less than 21 mm on CT), severe aortic annulus calcification, concomitant cardiac surgery, or other factors indicating high surgical risk. Patients with aortic regurgitation as the primary condition or significant calcification in the left ventricular outflow tract were not considered suitable for RD AVR. The surgeon's preference also influenced this decision.

And, by measuring the annulus diameter and perimeter, as well as the left ventricular outflow tract diameter and perimeter through pre-operative CT, we aimed to estimate the appropriate valve size in advance.

Changes in the text: see Page 6, line 112~118
“RD AVR was preferred for patients with aortic stenosis as the primary pathology, small aortic annulus (less than 21m on computed tomography), severe aortic annulus calcification, concomitant cardiac surgery, or other factors indicating high surgical risk (14). Individuals presenting with aortic regurgitation as the primary condition or exhibiting severe calcification in the left ventricular outflow tract (LVOT) were not considered candidates for RD AVR. Surgeon preference also played a role in this decision.”

15. Methods – Surgical Technique: Please clarify how many sutures were used in the bicuspid technique. Line 105 – “Additional” needs to be defined. Three nadir, plus three more? Or plus 6 more? The way it is written, it seems that you basically sewed in the Intuity with just a few less sutures than a 21mm surgical valve would require.

Reply:
That's a great question. When adding "additional stitches," depending on the degree of oval shape of the aortic valve, there are cases where an additional 3 to 6 stitches are added beyond the existing 3 nadir stitches. However, in almost all cases, about three additional stitches were sufficient. The reason not to spare additional sutures is that achieving a proper fit on the annular plane during prosthetic valve implantation is crucial.

Changes in the text: see Page 7, line 132
“, usually about three,”

16. Line 128, what definition of PVL was used? VARC-3? American Soc of Echo?

Reply:
Thank you for the detailed question. The definition of paravalvular leakage used in this study was based on the literature according to Zoghbi et al., and it was graded and assessed accordingly. However, in this study, there were no patients with postoperative regurgitation of mild severity or higher.
[Zoghbi WA, Jone PN, Chamsi-Pasha MA, Chen T, Collins KA, Desai MY, Grayburn P, Groves DW, Hahn RT, Little SH, Kruse E, Sanborn D, Shah SB, Sugeng L, Swaminathan M, Thaden J, Thavendiranathan P, Tsang W, Weir-McCall JR, Gill E. Guidelines for the Evaluation of Prosthetic Valve Function With Cardiovascular Imaging: A Report From the American Society of Echocardiography Developed in Collaboration With the Society for Cardiovascular Magnetic Resonance and the Society of Cardiovascular Computed Tomography. J Am Soc Echocardiogr. 2024 Jan;37(1):2-63.]

Changes in the text: see Page 20, line 424
“17. Zoghbi WA, Jone PN, Chamsi-Pasha MA, et al. Guidelines for the Evaluation of Prosthetic Valve Function With Cardiovascular Imaging: A Report From the American Society of Echocardiography Developed in Collaboration With the Society for Cardiovascular Magnetic Resonance and the Society of Cardiovascular Computed Tomography. J Am Soc Echocardiogr. 2024;37:2-63.”

17. Results section - See the comment above regarding the presentation of data in a consistent order – A vs B, C vs D throughout the entire manuscript. Make it easy for the reader to understand.

Reply:
Thank you for the valuable suggestion. To enhance clarity, I have modified the labeling of the type 0 bicuspid patient group from 'D' to 'B0' and the other types of bicuspid patients from 'C' to 'B1'.

18. Be careful with identifying statistically significant differences that may be clinically irrelevant. Line 150 – 152: The patients were all “low risk” based on EuroScore II and STS PROM.

Reply:
I agree with your statement. The patients in our study mostly had a low surgical risk. While the statistical difference between the two groups may not have significant clinical implications, we have described the results as they were presented. This is influenced by our institution's multidisciplinary discussions on aortic stenosis treatment, wherein patients with comparatively low surgical risk are primarily selected for surgical aortic valve replacement. Hence, I will elaborate on the mentioned points in the discussion section.

Changes in the text: see Page 14, line 290~293
“Reviewing the surgical risk profile of the patients in this study, the average value indicates a low-risk scenario. It is worth mentioning that in our institution's multidisciplinary discussions on the treatment strategy for aortic stenosis, patients predominantly classified as low surgical risk frequently choose surgical aortic valve replacement.”

19. Line 166 – 167 – The use of “was found in” or “not found in” is awkward. The outcomes/events “occurred” or “did not occur”.

Changes in the text: see Page 10, line 198
“occurred”

20. Secondary Analysis – this section should be removed. Comparing 6 patients to 8 patients – all of whom were carefully selected is highly subject to bias. With the addition of concomitant procedures in 66.7% of the D group, you are comparing apples

to oranges.

Reply:
I concur with your viewpoint. However, the purpose of conducting subgroup analysis is not to discover additional statistical significance but to present pre- and postoperative data separately for type 0 bicuspid patients and other bicuspid patients, aiming to highlight their unique characteristics. Specifically, in the case of type 0, there is still a scarcity of evidence supporting the application of RD AVR, and there are challenges in the surgical technique. Our aim was to demonstrate the feasibility of RD AVR in type 0 bicuspid aortic valves, even within small single centers with limited cardiac surgery volume.

Changes in the text: see Page 15, line 313~316
"The purpose of performing subgroup analysis is not to discover additional statistical significance but to present the pre- and postoperative data separately for type 0 bicuspid patients and other bicuspid patients, aiming to demonstrate their distinct characteristics."

21. Line 206 – your reference #20 is too old to be meaningful. Use the results of the large RCTs here PARTNER III and Evolut Low Risk.

Reply:
Thank you for your valuable input. The references you provided will be valuable additions to enhance the completeness of this paper. I will incorporate the literature you suggested.

Changes in the text: see Page 11, line 238~240
"In transcatheter AVR cases, the reported PPI rate ranges from approximately 6.5 to 17.4% (22, 23), and for bicuspid cases specifically, it is known to be in the range of 6.1 to 15.1% (24, 25)."

"22. Mack MJ, Leon MB, Thourani VH, et al. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. N Engl J Med. 2019;380:1695-705.

23. Popma JJ, Deeb GM, Yakubov SJ, et al. Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. N Engl J Med. 2019;380:1706-15.

24. Williams MR, Jilaihawi H, Makkar R, et al. The PARTNER 3 bicuspid registry for transcatheter aortic valve replacement in low-surgical-risk patients. JACC Cardiovasc

Interv. 2022;15:523-32.

25. Forrest JK, Ramlawi B, Deeb GM, et al. Transcatheter aortic valve replacement in low-risk patients with bicuspid aortic valve stenosis. JAMA Cardiol. 2021;6:50-7."

22. Line 209, reference 21 – this also needs to be updated to reflect what is known in 2024 regarding conduction disturbances after TAVR. The rates are even higher with AR – and no calcified leaflets are removed. A reference from 2012 is too old to be useful.

Reply:
I agree with your point. However, in the case of well-established and widely cited literature, the publication date may not necessarily be crucial. Therefore, I believe that important references can still be cited, even if they are relatively old, given their significance.

23. Following from #22, both TAVR Low-Risk trials had bicuspid registries. Please consider including the 30 days pacemaker rates from these studies for completion.

Reply:
Thank you for your insightful contribution. The references you shared will be valuable additions, contributing to the overall completeness of this paper. I will integrate the suggested literature into the document.

Changes in the text: see Page 11, line 238~240
"In transcatheter AVR cases, the reported PPI rate ranges from approximately 6.5 to 17.4% (22, 23), and for bicuspid cases specifically, it is known to be in the range of 6.1 to 15.1% (24, 25)."

24. Avoid verbose language such as "pivotal" and "critical" in the Discussion – let your data and findings speak. What is known? What is not known? How does your data fit into the body of knowledge?

Changes in the text: see Page 14, line 304
I replaced some adjectives such as "pivotal" and "crucial" with "important".

25. Line 256 – 260 – what data do you have to support these claims? TAVR in bicuspids has similar results to TAVR in tricuspid valves with newer generation devices. (Yoon et

al. 2017, and Low-risk trials mentioned above). There are no RCTs for bicuspid valves, but there is no reason to believe that just being bicuspid should warrant SAVR. Consider revising this paragraph significantly or removing it entirely.

Reply:
Yes, I agree with your opinion. The paragraph you pointed out is deemed as a controversial and unnecessary part. I will delete it. However, in the context of transcatheter aortic valve replacement, we included the paragraph speculating that many interventionists might still find it challenging in the case of Sievers type 0 bicuspid.

26. In your Conclusion – line 304 – avoid introducing new knowledge not supported by your data. You did not study aortic root geometry, did not discuss inclusion/exclusion criteria based on root geometry, and have no data in your manuscript to support this conclusion. Stick to what you studied and found. Then call for next steps – further study is needed to understand the utilization of RA AVR in specific BAV aortic root anatomy.

Reply:
Yes, I understand. The phrase "if the aortic root geometry is carefully considered" was added with the good intention of emphasizing the importance of considering the shape of the aortic annulus based on intraoperative findings. Since the geometry of the annulus differs between bicuspid and tricuspid cases, it is advisable to perform surgery with careful consideration of this aspect. I appreciate your valuable input, and I will modify it to avoid any potential misunderstanding. Also, thank you for pointing out that understanding 'the utilization of RA AVR in specific BAV aortic root anatomy' might require further research in the future.

Changes in the text: see Page 16, line 345
“the aortic root geometry” -> “the shape of the aortic annulus”

Reviewer B

In my opinion this manuscript lacks the novelty.
The issue that RD bioprostheses can be safely used in BAV patients is not new one. We can find a few articles, including original ones (1. Im S, Kim KH, Sohn SH, Kang Y, Kim JS, Choi JW. Comparable Outcomes of Bicuspid Aortic Valves for Rapid-Deployment Aortic Valve Replacement. J Chest Surg. 2023 Nov 5;56(6):435-444. doi: 10.5090/jcs.23.070. PMID: 37915291; PMCID: PMC10625967; 2. Coti I, Werner P,

Kaider A, Mach M, Kocher A, Laufer G, Andreas M. Rapid-deployment aortic valve replacement for patients with bicuspid aortic valve: a single-centre experience. Eur J Cardiothorac Surg. 2022 Sep 2;62(4):ezac017. doi: 10.1093/ejcts/ezac017. PMID: 35076066; 3. von der Linden J, Herrmann F, Belyaev S, Juchem G, Peterss S, Hagl C, Dashkevich A. Bicuspid Morphology and Rapid Deployment Valve Replacement: Is This Still a Contraindication? J Clin Med. 2023 Nov 29;12(23):7390. doi: 10.3390/jcm12237390. PMID: 38068441; PMCID: PMC10707038; etc) and at least one review (King M, Stambulic T, Payne D, Fernandez AL, El-Diasty M. The use of sutureless and rapid-deployment aortic valve prosthesis in patients with bicuspid aortic valve: A focused review. J Card Surg. 2022 Oct;37(10):3355-3362. doi: 10.1111/jocs.16795. Epub 2022 Jul 28. PMID: 35904115).
You must convince us or highlight these aspects of your paper that are real novel and true original.

Reply:
That's a valid observation. However, I believe that to create evidence, various types and levels of research need to come together, and the findings should be applicable even in small single centers. Similar studies, even if numerous, are crucial for potential use in future meta-analyses. While our research results may not hold significant statistical meaning, we find value in sharing our experience that bicuspid RD AVR (including Sievers type 0 bicuspid cases) can be successfully performed even in less-experienced centers.

Additionally, in our study, the inclusion of illustrations serves to distinctly detail the procedural nuances for RD AVR in Sievers type 0 bicuspid cases, which I consider to be one of the unique aspects. Furthermore, the technique involving additional stitches will captivate readers' interest.

In the discussion section you mentioned about PPM rate that was lower in the RD valves. For me this remark is obvious but adding such date it would make your paper clearer. Please add some info about rate of PPM in the discharge echocardiography among patients with RD prostheses.

Reply:
Out of the 30 patients who underwent RD AVR in this study, only one needed permanent pacemaker insertion, leading to a PPM rate of around 3.3%. I will incorporate this data into the discussion section.

Changes in the text: see Page 12, line 245~247
“In this study, among a total of 30 patients who underwent RD AVR, there was one case

of PPI (3.3%).”