

Peer review file

Article information: <https://dx.doi.org/10.21037/jtd-21-789>

Reviewer A

Comment 1. The title is, too broad, and thus unintentionally misleading. The title should reflect most closely that which mainly the focus in the content is. In my view, it appears that the authors have mainly focused on the efficacy and outcomes of valve sparing root replacement vs Bentall operation type valve replacement in Marfan syndrome. Therefore, the title should more reflect this perspective.

MFS, LDS, vascular Danlos etc as suggested by the authors are not similar genetic conditions and the aortopathies have varying implications accordingly. They are genetically distinct although the physical phenotype may express some similarities. Therefore, the title should be more focused to reflect this view. e.g., ~Marfan syndrome and other genetic origin connective tissue disorders presenting with root aneurysm or aortic dissection.

Reply 1. We agree. Therefore, we have considered the following title: "Systematic review and meta-analysis of aortic valve sparing surgery versus replacement surgery in ascending aortic aneurysms and dissection in patients with Marfan syndrome and other genetic connective tissue disorders."

Comment 2. Abstract: Page 2 line 38; Objective: ... sparing- versus replacement -type surgical; should be changed to valve sparing root replacement vs aortic root replacement. The meaning is implied but the terminology should be expanded in full.

Reply 2. We appreciate the observation. This has already been changed in the text.

Comment 3. A thorough revision by a language expert seems warranted.

Reply 3. The text has been thoroughly reviewed and corrected by a native English speaker who has been acknowledged by her name initials.

Comment 4. Page 3 63~86; The individual description of the various genetic conditions that may cause vascular diseases should be shortened as this is not the focus of the present review. One paragraph should suffice.

Reply 4. The Reviewer's suggestion was considered and the corrections have been made.

Comment 5. Page 3 87; “The history in the treatment of aortic damage could be feasible until”- should be changed to “could not be feasible~” Yes?

Reply 5. The Reviewer has made a good observation. The term "not" was missing and this has been added.

Comment 6. Page 3 91; “~ supracoronarian replacement technique~”; typographic error of supracoronarian which should be supracoronary.

Reply 6. We thank this observation. This was corrected.

Comment 7. Page 3 97; “It is until 1968, that Bentall and de Bono describe the technique”; should be past tense. “It is until~” should be It was not until 1968~. Yes?

Reply 7. This observation is correct and we have made the corresponding correction.

Comment 8. The more widely accepted abbreviation for Marfan syndrome has been MFS and MS was used more commonly for mitral stenosis. Perhaps the authors would

like to consider this for the sake of minimizing confusion.

Reply 8. We agree with this comment and the “MFS” abbreviation has been adopted for Marfan syndrome.

Comment 9. P3-4 lines 87~107. The history of root replacement and how David procedure had come to pass should also be shortened to one paragraph. This is well known and does not require an extensive historical review.

Reply 9. This was shortened as suggested and only one paragraph was left in the text.

Comment 10. In page 17 of figure 3, freedom from re-intervention overwhelmingly favored valve replacement type (as opposed to valve sparing) root replacement. One of the main causes for valve sparing root replacement failure, especially in patients with connective tissue disorder was related to annular dilatation and significant AI recurrence, especially after the root remodeling procedure that was first introduced by Magdi Yacoub. The technique had evolved to include an annuloplasty ring as described by Emanuel Lansec. Were there any papers in which the predominant repair method was by the root remodeling method without aortic annuloplasty ring implantation? Inclusion of series involving the Florida sleeve operation also poses confounding issues because this technique is not easily reproducible and is not accepted as a standard option. All remodeling type replacements acceptable for inclusion should be according to the Lansec type with an aortic annuloplasty ring.

Reply 10. We greatly appreciate the Reviewer's comment. Certainly, in this meta-analysis we found nine articles that used the surgical technique and annuloplasty. Details are now included in the Discussion.

Comment 11. Most papers dealing with aortic valve sparing root replacement or Bentall procedure, may include only a small volume of Marfan and other connective tissue

disorder patients with the majority of patients not having genetic disorders. In this case, the title and the content of this meta-analysis review may not necessarily reflect the outcomes of root surgery in genetic aortopathy patients. This should be checked.

Reply 11. The articles included in this series did contain a good number of patients with Marfan syndrome, although the number of other genetic disorders is much smaller.

Comment 12. For the valve sparing group, it would be useful to mention freedom from moderate to severe AR overtime versus reintervention/reoperation as the presence of severe AR does not necessarily lead to reintervention/reoperations.

Reply 12. We agree with this comment. In fact, data was originally mentioned in the table. We apologize for some misspellings that could have precluded the interpretation. Aortic insufficiency (or AR) of any grade was used because not all authors specified grade. For both valve sparing and valve replacement groups, the following are mentioned in the table: aortic insufficiency rate, valve reintervention rate, survivor rate without aortic insufficiency and survivor rate without valve intervention. Changes in Table 2 have been highlighted.

Comment 13. From the outset, the authors included dissection and aneurysm patients. Since the data is available, it would be useful to conduct a subanalysis of patients with dissection and aneurysmal etiology separately to reflect on the different implications of each.

Reply 13. Indeed, patients with dissection and aneurysm were considered. However, only one of the studies included (Bernhardt et al, 2011) stratified outcomes based on this distinction (according to such study, no differences were noted in its limited sample). Therefore, we were not able to conduct this analysis and we could only report the proportion of patients with dissection and aneurysm in each group (Table 2). This limitation has been acknowledged in the Discussion section. Additionally, due to an omission, the proportion of patients with aneurysm in each group had been left out, but

this has been corrected.

Comment 14. The authors should include their perspectives and viewpoints regarding the implications of the different types of surgeries based on the outcomes of the present analysis in more detail. What is the current trend looking into the future and how the roles of the different surgery types may be relevant in different situations?

Reply 14. We appreciate the comment of the Reviewer and we have made changes in the Discussion.

Reviewer B

Comment 1. I believe that the presentation and the discussion of the data needs to be improved. The discussion is very short, and should include how these data reflect current guidelines.

Reply 1. We appreciate the observation and have made the corrections in the Discussion.

Comment 2. What should be done in small centers where a David procedure is a rare event? Is aortic surgery in Marfans for every surgeon?

Reply 2. Given the complexity of aortic pathology (aneurysm / dissection of the aortic arch and thoracic / abdominal aorta) in every patient, highly specialized surgical treatments with input from experienced surgeons are required. We have added this discussion in the corresponding section.

Comment 3. Root sparing surgery is a no go in Marfans and could be mentioned. There are so many issues that could be included to make this paper more relevant. The

introduction is almost two pages and the discussion is only half a page. Should be the other way around

Reply 3. We greatly appreciate your comment. The Introduction was shortened and the Discussion was broadened.

Comment 4. Minor: Many things are not spelled correctly. I am not a native English writer but I use the spell check function on my computer.

Reply 4. The text has been thoroughly reviewed and corrected by a native English speaker who has been acknowledged by her name initials.