Peer review file

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Reviewer A

Comment 1: Please clarify the term "early mortality". Is it 30-day mortality? intra-op mortality? peri-op mortality?

Reply 1: Thank you for your comment. In our article, “early mortality” was defined as “30-day mortality” and “in-hospital mortality”. We included nine studies in the analysis of early mortality totally. Among them, three studies provided the 30-day mortality (1-3) and three provided the in-hospital mortality (4-6). In the remaining three studies, no early mortality occurred during follow-up. Considering that in most of clinical researches, both 30-day mortality and in-hospital mortality were widely used and reasonably represent the early mortality, we included both for further analysis. To clarify the term “early mortality”, we have modified the results subsection as follows: **(see manuscript Page 10, line 181)**

Results

Early mortality included 30-day mortality and in-hospital mortality.

Reference

1. Klotz S, Stock S, Sievers HH, Diwoky M, Petersen M, Stierle U, et al. Survival and reoperation pattern after 20 years of experience with aortic valve-sparing root replacement in patients with tricuspid and bicuspid valves. The Journal of thoracic and cardiovascular surgery. 2018;155(4):1403-11.e1.

2. Kallenbach K, Kojic D, Oezsoez M, Bruckner T, Sandrio S, Arif R, et al. Treatment of ascending aortic aneurysms using different surgical techniques: a single-centre experience with 548 patients. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery. 2013;44(2):337-45.

3. Subramanian S, Leontyev S, Borger MA, Trommer C, Misfeld M, Mohr FW. Valve-sparing root reconstruction does not compromise survival in acute type A aortic dissection. The Annals of thoracic surgery. 2012;94(4):1230-4.

4. Matalanis G, Shi WY, Hayward PA. Correction of leaflet prolapse extends the spectrum of patients suitable for valve-sparing aortic root replacement. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery. 2010;37(6):1311-6.
5. Svensson LG, Deglurkar I, Ung J, Pettersson G, Gillinov AM, D'Agostino RS, et al. Aortic valve repair and root preservation by remodeling, reimplantation, and tailoring: technical aspects and early outcome. Journal of cardiac surgery. 2007;22(6):473-9.
6. Graeter TP, Aicher D, Langer F, Wendler O, Schafers HJ. Mid-term results of aortic valve preservation: remodelling vs. reimplantation. The Thoracic and cardiovascular surgeon. 2002;50(1):21-4.

Comment 2: Did you find any information in articles regarding post-op neurological dysfunction (stroke, TIA....)? Did the rate of post-op neurological dysfunction have deference between two techniques?

Reply 2: Thank you for your suggestion. Indeed, postoperative neurological dysfunction can greatly influence the outcome of patients and it's of great significance to compare the difference between reimplantation and remodeling techniques, if possible. We reread the included article and find that five studies (1-3, 5, 7) provided the information of postoperative stroke. The result was shown in the Figure 5. No evidence of heterogeneity ($p = 0.72$; $I^2 = 0\%$) and no significant difference were observed in postoperative stroke between the reimplantation group and remodeling group (random effects model, RR = 1.26; 95%CI, 0.58–2.75; $p = 0.56$).

We have modified the results as follows: **(see manuscript Page 11, line 214)**

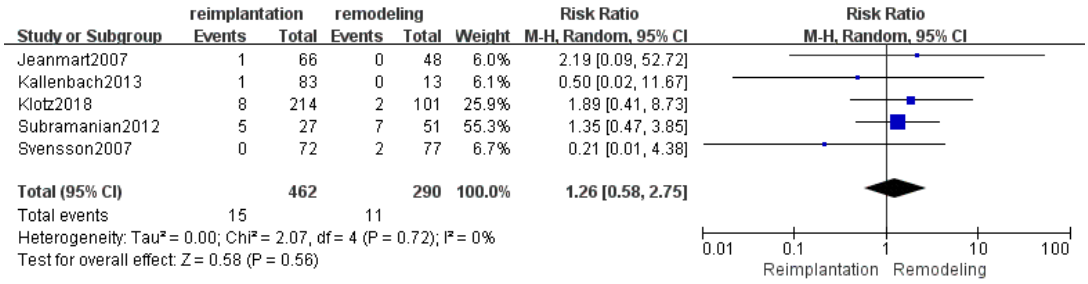
Results

Postoperative stroke

The results of postoperative stroke are shown in Figure 3C. Five studies (752 patients: 462 with reimplantation and 290 with remodeling) were included in the analysis of postoperative stroke. No evidence of heterogeneity ($p = 0.72$; $I^2 = 0\%$) and no significant difference were observed in postoperative stroke between the reimplantation group and remodeling group (random effects model, RR = 1.26; 95%CI, 0.58–2.75; $p = 0.56$).

The following figure was added in the Figure 6:

Figure 6. Forest plot showing the results of postoperative stroke with reimplantation and remodeling. (M-H = Mantel-Haenszel; CI = confidence interval.)



Reference

1. Klotz S, Stock S, Sievers HH, Diwoky M, Petersen M, Stierle U, et al. Survival and reoperation pattern after 20 years of experience with aortic valve-sparing root replacement in patients with tricuspid and bicuspid valves. The Journal of thoracic and cardiovascular surgery. 2018;155(4):1403-11.e1.

2. Kallenbach K, Kojic D, Oezsoez M, Bruckner T, Sandrio S, Arif R, et al. Treatment of ascending aortic aneurysms using different surgical techniques: a single-centre experience with 548 patients. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery. 2013;44(2):337-45.

3. Subramanian S, Leontyev S, Borger MA, Trommer C, Misfeld M, Mohr FW. Valve-sparing root reconstruction does not compromise survival in acute type A aortic dissection. The Annals of thoracic surgery. 2012;94(4):1230-4.

5. Svensson LG, Deglurkar I, Ung J, Pettersson G, Gillinov AM, D'Agostino RS, et al. Aortic valve repair and root preservation by remodeling, reimplantation, and tailoring: technical aspects and early outcome. Journal of cardiac surgery. 2007;22(6):473-9.

7. Jeanmart H, de Kerchove L, Glineur D, Goffinet JM, Rougui I, Van Dyck M, et al. Aortic valve repair: the functional approach to leaflet prolapse and valve-sparing surgery. The Annals of thoracic surgery. 2007;83(2):S746-51; discussion S85-90.

Comment 3: Did you find the 30-day mortality rate after re-operation? Did the 30-day

mortality rate have difference between two techniques?

Reply 3: Thank you for your suggestion. According to previous published studies, reoperation on the ascending aorta and aortic root had a relatively higher operative mortality than primary aorta procedures and hospital mortality for reoperation varied between 6% and 19% (8-11). However, there is scarcely any articles compared the mortality for reoperation between reimplantation and remodeling. Based on our results, the reoperation rate in the remodeling group was almost three times higher than the reimplantation group but none of included studies has reported the 30-day mortality rate after reoperation. The discussion on the surgical procedure and prognosis of reoperation of aortic root aneurysms is important, which is expected to be answered in future studies.

We have modified the discussion as follows: **(see manuscript Page 14, line 263)**

Discussion

According to previous published studies, reoperation on the ascending aorta and aortic root had a relatively higher operative mortality than primary aorta procedures and hospital mortality for reoperation varied between 6% and 19%. However, there is scarcely any articles compared the mortality for reoperation between reimplantation and remodeling, which is expected to be answered in future studies.

Reference

8. Schepens MA, Dossche KM, Morshuis WJ. Reoperations on the ascending aorta and aortic root: pitfalls and results in 134 patients. The Annals of thoracic surgery. 1999;68(5):1676-80.

9. Malvindi PG, van Putte BP, Heijmen RH, Schepens MA, Morshuis WJ. Reoperations on the aortic root: experience in 46 patients. The Annals of thoracic surgery. 2010;89(1):81-6.

10. Silva J, Maroto LC, Carnero M, Vilacosta I, Cobiella J, Villagrán E, et al. Ascending aorta and aortic root reoperations: are outcomes worse than first time surgery? The Annals of thoracic surgery. 2010;90(2):555-60.

11. Luciani N, De Geest R, Anselmi A, Glieca F, De Paulis S, Possati G. Results of reoperation on the aortic root and the ascending aorta. The Annals of thoracic surgery.

2011;92(3):898-903.

Comment 4: Did you find any information in articles regarding readmission rate due post-op AR or MACCE in the two techniques?

Reply 4: Thank you for your suggestion. The readmission rate due to postoperative AR or MACCE is an important index to exhibit the prognosis of patients. However, most studies only reported the reoperation rate and none of included studies has reported the readmission rate. Further investigation was warranted regarding readmission rate in this population.

Reviewer B

Comment 1: Authors demonstrated meta-analysis of outcomes following reimplantation versus remodeling techniques for aortic root aneurysms. Late mortality and freedom from reoperation were superior in reimplantation technique over remodeling one. My concern is that the current study has included some ones including small number of patients who had undergone either technique and etiologies of acute aortic dissection and only Marfan syndrome. This concern would have affected outcomes. It is reasonable to assume that surgeons with few experiences cannot achieve good outcomes. Also, emergency surgery affects quality of surgery, especially performed after hours or at night…Therefore, we cannot draw conclusions. Authors should have focused on only aortic root aneurysm to perform meta-analysis on reimplantation versus remodeling techniques. It would be reasonable to make some comments after meta-analysis.

Reply 1: Thank you for your comment and suggestion. When we designed our study, we have also considered whether we should include patients with Marfan syndrome or acute type A dissection. Considering aortic root aneurysms combing with Marfan syndrome or acute type A dissection might have poorer prognosis (12, 13), the ideal meta-analysis should pay attention to the difference between various etiology of aortic root aneurysms including bicuspid-valve, Marfan syndrome and dissection aneurysms. However, as shown in table 2, most studies included both Marfan and non-marfan patients and the percentage of Marfan patient varied from different

studies. Some studies also included patients with acute dissection (6). Among all included articles, only Sheick-Yousif compare the difference between reimplantation and remodeling in different etiology and reported that Marfan and aortic dissection patients had significantly higher early mortality when undergoing the remodeling technique (7.6% vs. 0% in marfan; 6.7% vs. 1.1% in aortic dissection) (14). Therefore, analysis of patient groups with specific etiology were hard to perform. Although all previous meta-analysis and systemic review had included articles about only Marfan syndrome or acute type A dissection in their studies, we agreed with the reviewer that it is necessary to analyze their outcomes separately based on the etiology. On the basis of all 14 included studies (including a newly-added non-English study written in Hebrew suggested by other reviewers), we performed a subgroup analysis of Marfan syndrome as well as acute type A dissection separately and the results indicated that the conclusion was similar as before despite of the etiology. However, it should be noticed that in the studies not focusing on specific etiology, Marfan syndrome and AAAD patients were also included, more or less. We were unable to obtain etiology information from all enrolled articles and had to perform subgroup analysis within limited studies available of the outcomes of patient groups with specific etiology (3, 15-17). Thus the results of subgroup analysis should be interpreted with caution.

We agreed with the reviewer that both experience of surgeons and emergency surgery can affect the outcomes. Considering the nature of retrospective study, confounding factors can hardly be adjusted and we will discussed it in the limitation part of discussion.

The Methods has been modified as follows: **(see manuscript Page 8, line 147)**

Subgroup analysis of marfan syndrome and acute type A dissection was performed in studies of patients with specific etiology.

The discussion has been modified as follows: **(see manuscript Page 16, line 307)**

We need to acknowledge that our study has some limitations. First, our study was based on retrospective observational cohort studies. Baseline information, selection criteria and surgical indications varied across different centers. Both the experience

of surgeons and emergency surgery can affect the outcomes. Due to the nature of retrospective observational studies, it's unlikely that the all bias and heterogeneity resulted from above problems can be adjusted or eliminated. Second, the time period for patients who underwent surgeries spanned from 1988 to 2016. Although all included studies were followed up for more than one year, the difference of follow-up time between institutions can hardly be balanced, neither can we set a specified time-point (for example, 5-year follow-up) for further analysis. Additionally, the mean follow-up time for all included studies was limited to less than 10 years, and some were less than 5 years, which make it unlikely for long-term mortality and complications to be evaluated. Therefore, further investigation and longer follow-up data are warranted so that the outcomes of certain techniques can be fully assessed. Third, considering the limited information of etiology and pathology provided by included studies, we were unable to obtain etiology information from all articles and subgroup analysis could only performed within limited studies available of the outcomes of patient groups with specific etiology. The results of subgroup analysis should be interpreted with caution. Future researches with the accumulation of relevant research data and the extension of follow-up time may be able to answer the above mentioned questions more accurately.

The figures have been replaced as follows:

Figure 4. Forest plot showing the results of (A) early mortality and (B) late mortality with reimplantation and remodeling. (M-H = Mantel-Haenszel; CI = confidence interval.)

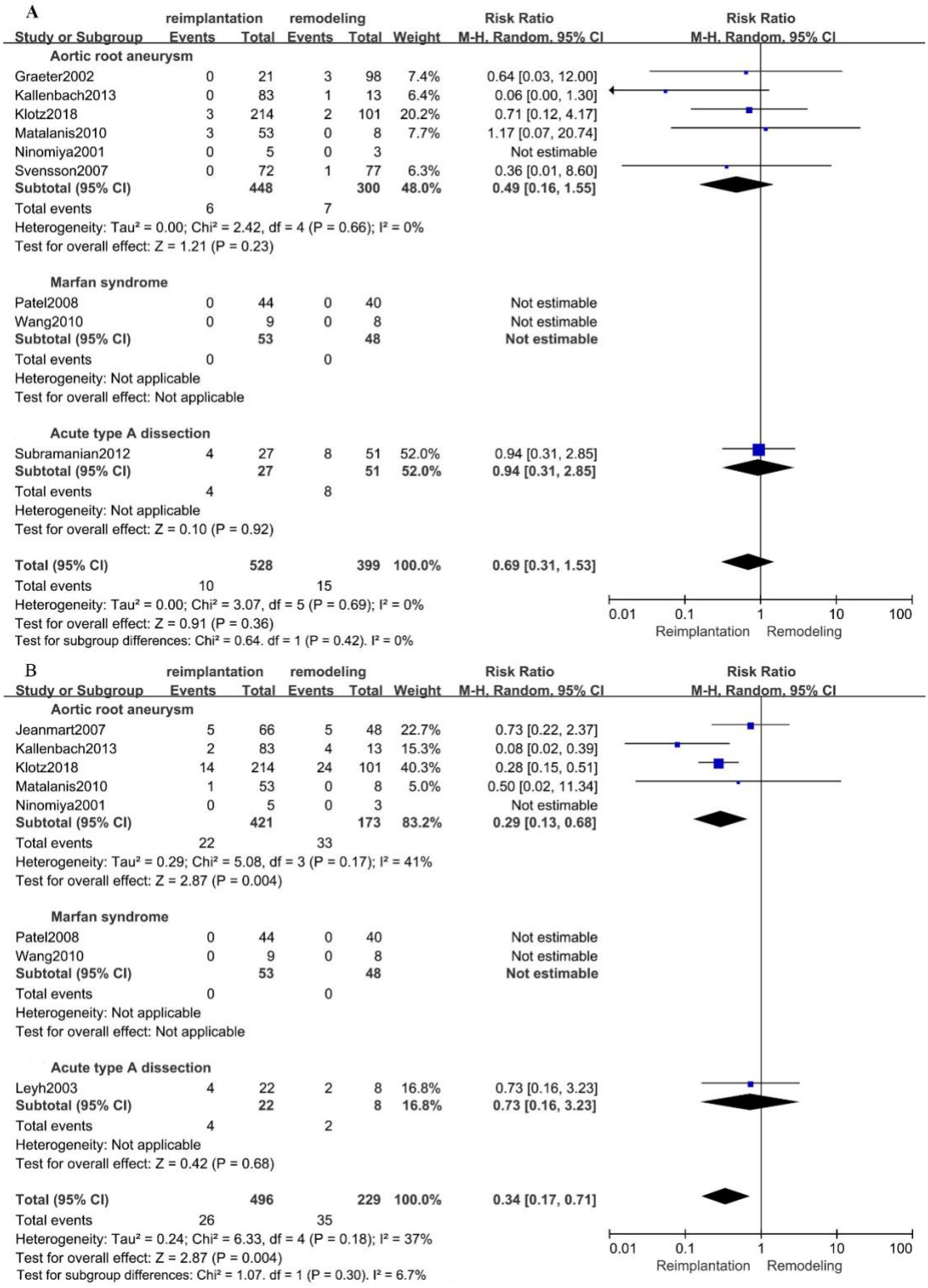
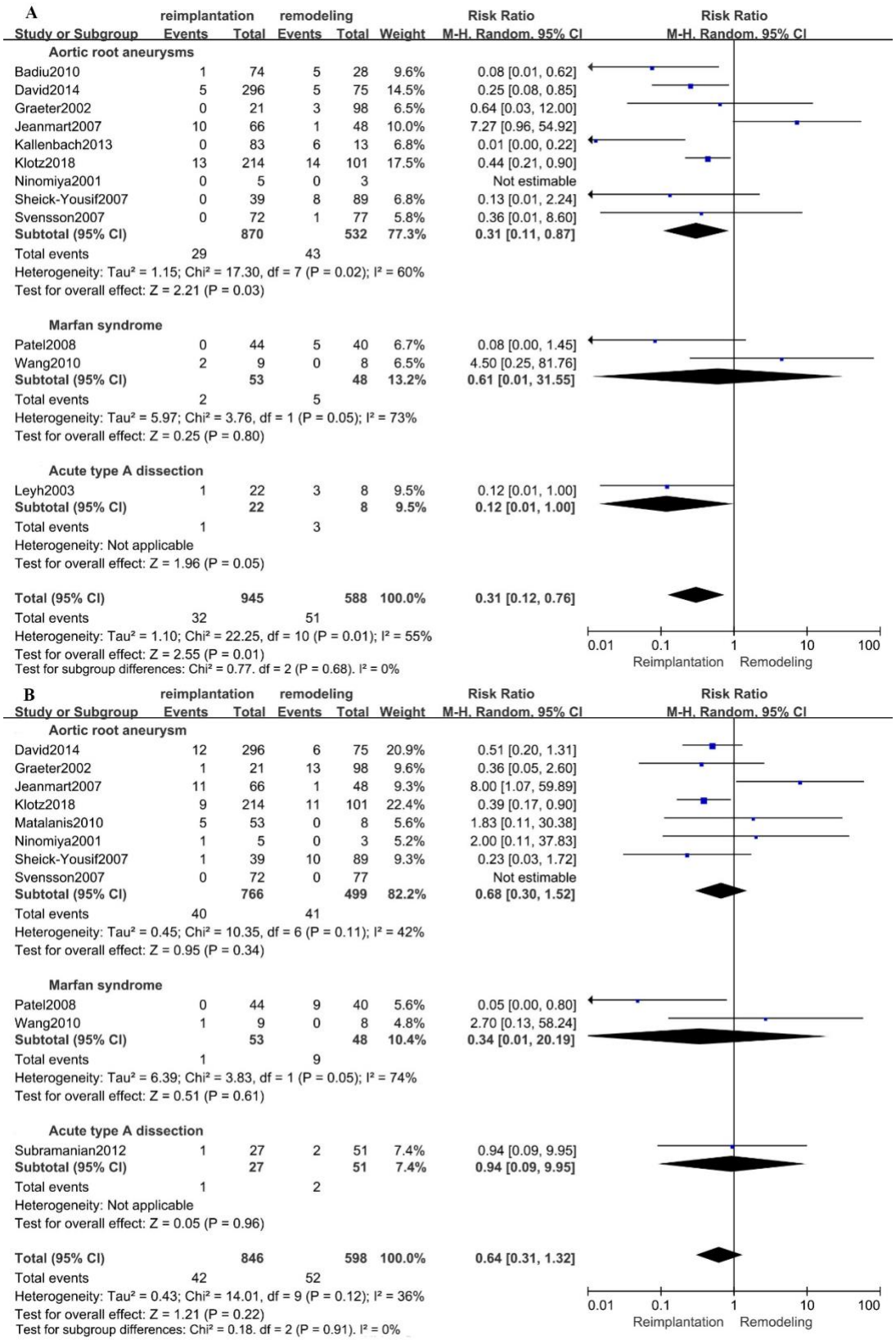


Figure 5. Forest plot showing the results of (A) reoperation, (B) postoperative moderate to severe aortic regurgitation (AR) with reimplantation and remodeling. (M-H = Mantel-Haenszel; CI = confidence interval.)



Reference

3. Subramanian S, Leontyev S, Borger MA, Trommer C, Misfeld M, Mohr FW. Valve-sparing root reconstruction does not compromise survival in acute type A

aortic dissection. The Annals of thoracic surgery. 2012;94(4):1230-4.

6. Graeter TP, Aicher D, Langer F, Wendler O, Schafers HJ. Mid-term results of aortic valve preservation: remodelling vs. reimplantation. The Thoracic and cardiovascular surgeon. 2002;50(1):21-4.

12. Elsayed RS, Cohen RG, Fleischman F, Bowdish ME. Acute Type A Aortic Dissection. Cardiology clinics. 2017;35(3):331-45.

13. Zehr KJ, Orszulak TA, Mullany CJ, Matloobi A, Daly RC, Dearani JA, et al. Surgery for aneurysms of the aortic root: a 30-year experience. Circulation. 2004;110(11):1364-71.

14. Sheick-Yousif B, Shinfeld A, Tager S, Priesman S, Smolinsky AK, Raanani E. [Aortic valve sparing surgery]. Harefuah. 2007;146(11):849-53, 910.

15. Leyh RG, Fischer S, Kallenbach K, Kofidis T, Pethig K, Harringer W, et al. High failure rate after valve-sparing aortic root replacement using the "remodeling technique" in acute type A aortic dissection. Circulation. 2002;106(12 Suppl 1):I229-33.

16. Patel ND, Weiss ES, Alejo DE, Nwakanma LU, Williams JA, Dietz HC, et al. Aortic root operations for Marfan syndrome: a comparison of the Bentall and valve-sparing procedures. The Annals of thoracic surgery. 2008;85(6):2003-10; discussion 10-1.

17. Wang R, Ma WG, Tian LX, Sun LZ, Chang Q. Valve-sparing operation for aortic root aneurysm in patients with Marfan syndrome. The Thoracic and cardiovascular surgeon. 2010;58(2):76-80.

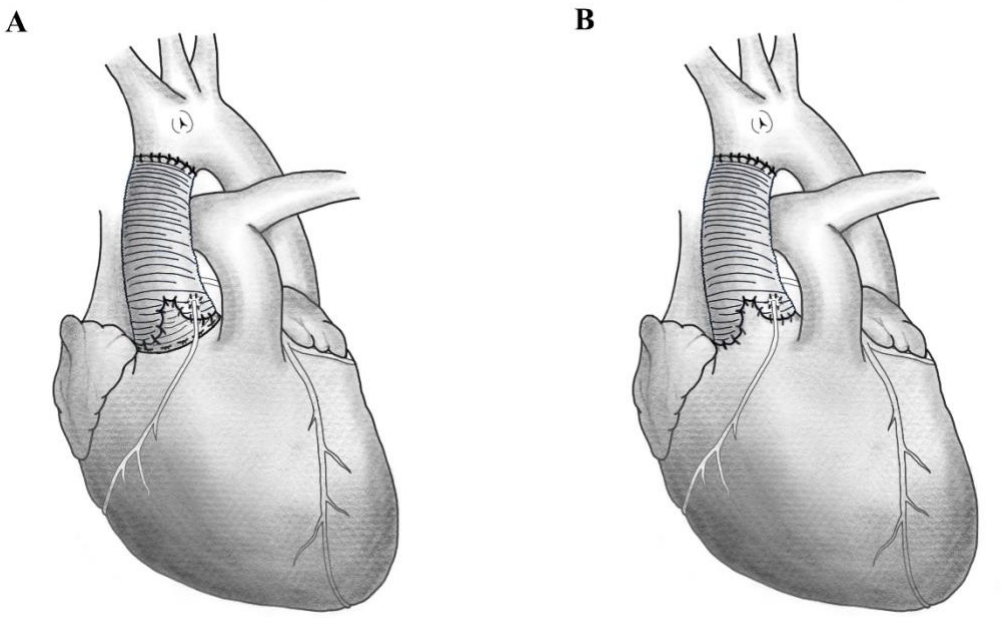
Reviewer C

Comment 1: The authors should include a schematic diagram illustrating the difference between remodeling and reimplantation.

Reply 1: Thank you for your suggestion. We have provided an additional diagram in Figure1, which can help the readers learn the difference between these two techniques more clearly.

The figure 1 has been added in the manuscript as follows:

Figure 1. Schematic diagram illustrating (A) the reimplantation and (B) remodeling techniques.



Comment 2: The studies seem to be fairly consistent in reporting increased pump times and clamp times for reimplantation vs revmodeling, as expected. However, the trend, if any, appears to favor reimplantation for early mortality. Although the risk ratio overlaps the line of unity, this observation should be at least mentioned in the discussion, as it appears to be paradoxical.

Reply 2: Thank you for your comment. As you mentioned, although no significant difference was observed in the early mortality between two groups, the trend seem to favor the reimplantation technique (random effects model, RR = 0.69; 95%CI, 0.31–1.53; p = 0.36), which was contradictory with the results of CPB time and aortic clamping time because normally patients with longer operative ischemic time seem to have higher risk of early mortality (18). Although remodeling had a shorter CPB time, it is reported that remodeling technique was associated with higher risk of operative bleeding because of the difference of suture method (19), which may explain the relatively higher early mortality in remodeling groups. With the development of extracorporeal circulation and myocardial protection techniques, the CPB time was no

longer the only determinant factor of mortality. Other factors like age, sex and comorbidities may also affect the outcomes (20). The result of our study did not show significant difference between two groups therefore we cannot conclude that reimplantation was superior in lower early mortality than remodeling.

We have modified the discussion as follows:

Although no significant difference was observed in early mortality, postoperative moderate to severe AR and postoperative stroke between two groups, the trend appeared to favor reimplantation technique for early mortality and postoperative AR. **(see manuscript Page 12, line 233)**

It seemed to be paradoxical that reimplantation, which had longer CPB time and aortic clamping time, appeared to have better trend in early outcomes than remodeling. Remodeling was reported to have higher risk of operative bleeding because of the difference of suture method, which may explain the relatively higher early mortality. With the development of extracorporeal circulation and myocardial protection techniques, CPB time was no longer the determinant factor of mortality. Other factors like age, sex and comorbidities also influenced the early outcomes. However, significant difference in early mortality was not observed between two groups therefore we cannot draw the conclusion that remodeling was associated with higher early mortality. **(see manuscript Page 15, line 287)**

Reference

18. Wesselink RM, de Boer A, Morshuis WJ, Leusink JA. Cardio-pulmonary-bypass time has important independent influence on mortality and morbidity. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery. 1997;11(6):1141-5.

19. David TE, Maganti M, Armstrong S. Aortic root aneurysm: principles of repair and long-term follow-up. The Journal of thoracic and cardiovascular surgery. 2010;140(6 Suppl):S14-9; discussion S45-51.

20. Goldfinger JZ, Halperin JL, Marin ML, Stewart AS, Eagle KA, Fuster V. Thoracic aortic aneurysm and dissection. Journal of the American College of Cardiology. 2014;64(16):1725-39.

Comment 3: The duration of follow-up for the studies needs to be mentioned when considering long term mortality.

Reply 3: Thanks for the comment. As shown in the Table 1, the mean follow-up time for all included studies varied from 1.5 years to 8.9 years. Although all included studies were followed up for more than one year, considering the nature of retrospective observational cohort study, the difference of follow-up between all institutions cannot be balanced and we cannot set a time-point like 5-year to limit the follow-up time. We admitted the bias resulted from this can hardly be avoided. With the accumulation of relevant research data and the extension of follow-up time, future research may be able to answer this question more accurately.

We have modified our discussion as followed: **(see manuscript Page 16, line 312)** *Second, the time period for patients who underwent surgeries spanned from 1988 to 2016. Although all included studies were followed up for more than one year, the difference of follow-up time between institutions can hardly be balanced, neither can we set a specified time-point (for example, 5-year follow-up) for further analysis. Additionally, the mean follow-up time for all included studies was limited to less than 10 years, and some were less than 5 years, which make it unlikely for long-term mortality and complications to be evaluated. Therefore, further investigation and longer follow-up data are warranted so that the outcomes of certain techniques can be fully assessed.*

Comment 4. The methodology of the studies is not discussed. Were survival analyses uniformly employed in them?

Reply 4: Thank you for your comment. Of all 14 enrolled studies, nine studies included the survival analysis and the remaining five (5, 14, 15, 17, 21) merely used descriptive statistical methods like chi-square test to analysis the data. All five studies not use survival analysis were published before 2010, when most respective studies did not conventionally include survival analysis. Nevertheless, in current study setting, we mainly extracted the original descriptive data from the results and tables in

the enrolled studies. Therefore whether the study used survival analysis or not would not influence our precision of data extraction or final conclusions.

Reference

5. Svensson LG, Deglurkar I, Ung J, Pettersson G, Gillinov AM, D'Agostino RS, et al. Aortic valve repair and root preservation by remodeling, reimplantation, and tailoring: technical aspects and early outcome. Journal of cardiac surgery. 2007;22(6):473-9.

15. Leyh RG, Fischer S, Kallenbach K, Kofidis T, Pethig K, Harringer W, et al. High failure rate after valve-sparing aortic root replacement using the "remodeling technique" in acute type A aortic dissection. Circulation. 2002;106(12 Suppl 1):I229-33.

17. Wang R, Ma WG, Tian LX, Sun LZ, Chang Q. Valve-sparing operation for aortic root aneurysm in patients with Marfan syndrome. The Thoracic and cardiovascular surgeon. 2010;58(2):76-80.

20. Ninomiya M, Takamoto S, Kotsuka Y, Miyairi T, Morota T, Kubota H. Midterm results after aortic valve-sparing operation. The Japanese journal of thoracic and cardiovascular surgery : official publication of the Japanese Association for Thoracic Surgery = Nihon Kyobu Geka Gakkai zasshi. 2001;49(12):706-10.

Comment 5: Aortic regurgitation, reoperation, and death are competing risks in the long term follow-up. Can the authors report survival free of AR or reoperation?

Reply 5: Thank you for your suggestion. We admitted that survival free of reoperation or AR was a more potent indicator to represent the prognosis of patients. However, in retrospective studies, defining patients free of reoperation or AR needed rigorous follow-up. Unfortunately, among all 14 studies that we included, only five have reported freedom from reoperation(varied from 85% to 100% in reimplantation group; varied from 86.1% to 97% in remodeling group) (1, 6, 7, 15, 16) and three have reported freedom from postoperative moderate to severe AR (varied from 83% to 94.7% in reimplantation group; varied from 87% to 100% in remodeling group) (4, 6, 7), most of which only provided proportion instead of proportion and standard error,

which make it difficult to perform further analysis based on these limited data. However, the number of events occurred in reoperation and postoperative AR were reported in 11 studies, that's why we chose them for further analysis.

Reference

1. Klotz S, Stock S, Sievers HH, Diwoky M, Petersen M, Stierle U, et al. Survival and reoperation pattern after 20 years of experience with aortic valve-sparing root replacement in patients with tricuspid and bicuspid valves. The Journal of thoracic and cardiovascular surgery. 2018;155(4):1403-11.e1.

4. Matalanis G, Shi WY, Hayward PA. Correction of leaflet prolapse extends the spectrum of patients suitable for valve-sparing aortic root replacement. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery. 2010;37(6):1311-6.

6. Graeter TP, Aicher D, Langer F, Wendler O, Schafers HJ. Mid-term results of aortic valve preservation: remodelling vs. reimplantation. The Thoracic and cardiovascular surgeon. 2002;50(1):21-4.

7. Jeanmart H, de Kerchove L, Glineur D, Goffinet JM, Rougui I, Van Dyck M, et al. Aortic valve repair: the functional approach to leaflet prolapse and valve-sparing surgery. The Annals of thoracic surgery. 2007;83(2):S746-51; discussion S85-90.

14. Sheick-Yousif B, Shinfeld A, Tager S, Priesman S, Smolinsky AK, Raanani E. [Aortic valve sparing surgery]. Harefuah. 2007;146(11):849-53, 910.

15. Leyh RG, Fischer S, Kallenbach K, Kofidis T, Pethig K, Harringer W, et al. High failure rate after valve-sparing aortic root replacement using the "remodeling technique" in acute type A aortic dissection. Circulation. 2002;106(12 Suppl 1):I229-33.

16. Patel ND, Weiss ES, Alejo DE, Nwakanma LU, Williams JA, Dietz HC, et al. Aortic root operations for Marfan syndrome: a comparison of the Bentall and valve-sparing procedures. The Annals of thoracic surgery. 2008;85(6):2003-10; discussion 10-1.

Comment 6: It is also concerning that non-English language publications are

excluded. It would be helpful to include them if possible, or at least to mention their conclusions in the manuscript.

Reply 6: Thank you for your suggestion. We have reread the 6 excluded non-English articles, only one article from Israel written in Hebrew met the inclusion criteria (14). Sheick-Yousif and his colleagues reported that among 39 patients underwent reimplantation and 89 patients underwent remodeling, remodeling was associated with higher risk of reoperation (0/39 vs. 10/89) and postoperative AR(1/39 vs. 8/89). Therefore, we included it in our study and found the conclusion was same as before. The information of the newly-included article has been added to the Tables and Figures.

The results has been modified as follows: **(see manuscript Page 10, line 196)**

Reoperation rate

Reoperation included reoperations for aortic valve regurgitation, aortic valve endocarditis and aortic root abscesses during follow-up and did not include re-exploration for bleeding. The results of reoperation are shown in Figure 4A. Twelve studies (1533 patients: 945 with reimplantation and 588 with remodeling) were included in the analysis of reoperation. The results showed that the reoperation rate was much higher in the remodeling group than in the reimplantation group (random effects model, RR = 0.31; 95% CI, 0.12–0.76; p = 0.01). However, a high level of heterogeneity was indicated between studies (p = 0.01, I^2 = 55 %).

Postoperative moderate to severe AR

AR of grade 3 or greater was regarded as moderate to severe. We calculated the exact number of patients with postoperative moderate to severe AR when the study only provided data of freedom from moderate to severe AR. The results of postoperative AR are shown in Figure 4B. Eleven studies (1444 patients: 846 with reimplantation and 598 with remodeling) were included in the analysis of postoperative AR. No significant difference was shown between the two groups (random effects model, RR = 0.64; 95% CI, 0.31–1.32; p = 0.22; I^2 = 36%). No evidence of heterogeneity was observed (p = 0.12, I^2 = 36 %).

Reference

14. Sheick-Yousif B, Shinfeld A, Tager S, Priesman S, Smolinsky AK, Raanani E. [Aortic valve sparing surgery]. Harefuah. 2007;146(11):849-53, 910.

7. Did all the studies reporting long term follow-up data begin their reporting at the time of operation, or is there variability in determining time zero? If so, this might introduce an immortal time bias.

Response: Thank you for your comment. Although the starting point of follow-up was not mentioned in most included studies, usually the time of operation was regarded as the starting point of follow-up in most clinical researches. Even though there might be a slight deviation in the starting point of the follow-up (for example, very few researchers might choose the discharge date as the start of the follow-up), considering the much more longer follow-up time in the included studies, we believe that this deviation has very limit influence on our conclusion.