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Midterm Clinical Outcomes of Reimplantation Versus Remodeling Valve-Sparing Aortic Root Replacement in Patients With Connective Tissue Disorders: A Meta-Analysis

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This meta-analysis aimed to compare the midterm clinical outcomes of reimplantation versus remodeling techniques for valve-sparing aortic root replacement (VSARR) in patients with connective tissue disorders (CTDs). Studies were screened and identified after the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines from the PubMed, Web of Science, and Embase databases. Forest plots were produced using Review Manager 5.3 (Cochrane, UK). Studies comparing early and midterm clinical outcomes of reimplantation versus remodeling VSARR in patients with CTD with a mean age ≥18 years were included. The sensitivity analysis excluded studies and subgroups of patients that received ring or suture annuloplasty in addition to remodeling surgery. The study selection identified 9 eligible studies. After analysis of the study period and location for patient crossover, 7 retrospective studies consisting of 597 patients (301 reimplantation and 296 remodeling) were pooled. The pooling revealed no significant difference in postoperative mortality (estimated mean follow-up of 10.5 years) (odds ratio [OR] 0.66, 95% confidence interval [CI] 0.30 to 1.48, $I^2 = 30\%$, p = 0.32), reoperation (OR 0.35, CI 0.04 to 3.30, $I^2 = 81\%$, p = 0.36), or occurrence of postoperative aortic regurgitation of ≥2 (OR 0.56, CI 0.31 to 1.02, $I^2 = 47\%$, p = 0.06). The sensitivity analysis excluding annuloplasty demonstrated improved mortality (OR 0.19, CI 0.06 to 0.64, $I^2 = 0\%$, p = 0.007) and decreased aortic regurgitation of ≥2 (OR 0.23, CI 0.10 to 0.53, $I^2 = 47\%$, p = 0.0005) in reimplantation VSARR. The rates of reoperation remained insignificant in the sensitivity analysis (OR 0.43, CI 0.05 to 3.53, $I^2 = 71\%$, p = 0.43). In conclusion, this meta-analysis has demonstrated no significant difference in the midterm clinical outcomes of reimplantation versus remodeling techniques of VSARR. The sensitivity analysis excluding studies and patient subgroups that received remodeling and annuloplasty suggests remodeling alone to be inferior to reimplantation in patients with CTDs. Further research is required to assess remodeling and annuloplasty against reimplantation in patients of this demographic because the current body of knowledge does not allow sufficient analysis. **(Am J Cardiol 2024;213:28−35)**

Keywords: aortic root aneurysm, connective tissue disorder, reimplantation, remodeling, valve-sparing aortic root replacement

Connective tissue disorders (CTDs) are a group of genetic conditions that affect the function of the extracellular matrix, resulting in subsequent pathology of multiple systems, including the cardiovascular system. The most common of which is Marfan syndrome, an autosomal dominant condition associated with the FBN-1 genetic mutation that transcribes the fibrillin-1 extracellular matrix protein. Similar pathophysiologic patterns are observed in Ehlers-Danlos syndrome and Loeys−Dietz syndrome, inheritable conditions caused by collagen and transforming growth factor dysfunction, respectively.[1] Patients with CTDs often present with more severe aortopathy—including valvular regurgitation, aneurysmal dilation, and dissection—at a younger age, requiring alternative surgical consideration to patients without CTDs.[2,3] A total of 2 previous meta-analyses have compared the clinical outcomes of valve-sparing aortic root replacement (VSARR) versus composite valve grafts in patients with CTDs. In addition to the lack of anticoagulation burden, Flynn et al[4] and Soto et al[5] have demonstrated decreased rates of thromboembolic events and infective endocarditis in patients who underwent

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See page 34 for Declaration of Competing Interest.

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VSARR of this demographic. As a result of earlier diagnoses and improved aortic surveillance, patients with CTDs are more frequently offered prophylactic VSARR surgery, providing improved outcomes compared with nonelective surgery.[6,7] There is limited evidence and a lack of randomized data as to whether reimplantation of the native valve[8] or remodeling of the aortic root[9] produces superior clinical outcomes in patients with CTD. Many surgeons advocate for reimplantation techniques because of the perceived increased risk of annular dilation in remodeling VSARR despite the technique producing postoperative structures similar to native anatomy and preserving physiologic movements associated with the aortic root in systole and diastole.[10] A 2020 meta-analysis by Zhou et al[11] demonstrated improved rates of reoperation and aortic regurgitation and decreased mortality in reimplantation compared with remodeling VSARR in patients without CTDs.[11] However, the etiology of the included study population does not represent the demographic of patients with CTDs nor does it assess the implementation of structural annuloplasty in remodeling surgery. As a result of the recent increase in published data, we aimed to produce the first feasible meta-analysis comparing the clinical outcomes of reimplantation and remodeling VSARR surgery in adult patients with CTDs, with consideration given to developing surgical techniques.

Methods

Search strategy and selection criteria

PubMed, Web of Science, and Embase databases were used for preliminary study identification, using the search terms (["connective tissue disorder" OR "Marfan's syndrome"] AND "aortic root replacement") and reviewed in adherence with Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA).[12] The PRISMA guidelines and adherence evidence are available to view in the supplementary material. Studies that met the inclusion criteria were selected for review. The inclusion criteria required double-arm studies comparing reimplantation versus remodeling VSARR in patients with CTDs, with a mean age ≥18 years. Abstracts, conference presentations, case reports, editorials, expert opinions, and non-English language studies were excluded from screening.

Study selection and data extraction

Search results were screened by way of assessment of the study title/abstract, and full manuscripts were reviewed by the application of the aforementioned inclusion and exclusion criteria. Uncertainty or variation of study assessment was resolved by discussion. The outcomes were independently assessed for potential patient crossover by the evaluation of study data unit location and study periods. Priority was given to bias-treated data and more recently published in the event that study location and study period presented a high risk of patient crossover. The Newcastle−Ottawa scale was used to assess the quality of all included studies, with scores ≥6 of a potential 9 considered as high quality.[13] Funnel plot assessment was used to determine the risk of reporting and publication bias.[14] Analysis data were extracted from study text, tables, and figures, with raw figures calculated from percentages where available and necessary. The obtained study data include study period and location, method, surgical techniques, demographic, and patient outcomes. The use of structural annuloplasty in remodeling surgery was extracted from surgical technique data provided in the study methods. All clinical outcomes reported by a significant number of included studies were pooled for analysis. Early and midterm outcomes include in-hospital mortality, stroke, re-exploration for bleeding, long-term mortality, reoperation rates, and postoperative occurrence of aortic regurgitation. Sensitivity analysis was performed, excluding studies and patient subgroups that received suture or ring annuloplasties.

Statistical analysis

Statistical meta-analyses and forest plots were performed on Review Manager 5.3 by way of the Mantel−Haenszel test, producing odds ratios (ORs) for dichotomous data with a 95% confidence interval (CI).[15] Fixed-effects models were used where heterogeneity (I^2) was calculated to be <50%, with random effects used when I^2 ≥50%. Individual forest plots were calculated where 3 or more included studies reported postoperative clinical outcomes. Propensity score-matched and bias-treated data were prioritized where available.

Results

Search results

Initial study identification using search preliminary search terms (["connective tissue disorder" OR "Marfan's syndrome"] AND "aortic root replacement") produced 1,041 articles from PubMed, Web of Science, and Embase databases, March 2023. After the exclusion of 483 duplicates, 558 abstracts were screened for full manuscript analysis. Of the 35 studies examined for inclusion, 17 were excluded on the grounds of including an inappropriate patient population, either a mean patient age of <18 years or the absence of patients with CTDs. A total of 9 studies met the inclusion criteria for pooling; however, the assessment of the unit location and study period identified possible patient crossover. A subsequent prioritization of bias-treated and more recently published data resulted in the final inclusion of 7 observational studies (Figure 1). During subsequent research, a newly published study by David et al[16] was later identified, which provided more patient information from the same institution and study period as the included 2022 study by Elbatarny et al.[17] After discussion, we concluded that we would prioritize data from the previously published 2022 study because of the use of propensity score matching and subsequent reduction in selection bias. Quality assessment of the included studies evidenced all data to be high quality. The Newcastle−Ottawa scale assessment is visible in the attached Supplementary Material. Table 1[17−23] lists the characteristics of the included studies.

Outcomes

Five included studies reported long-term mortality in 435 patients with an estimated mean follow-up (EMFU) of

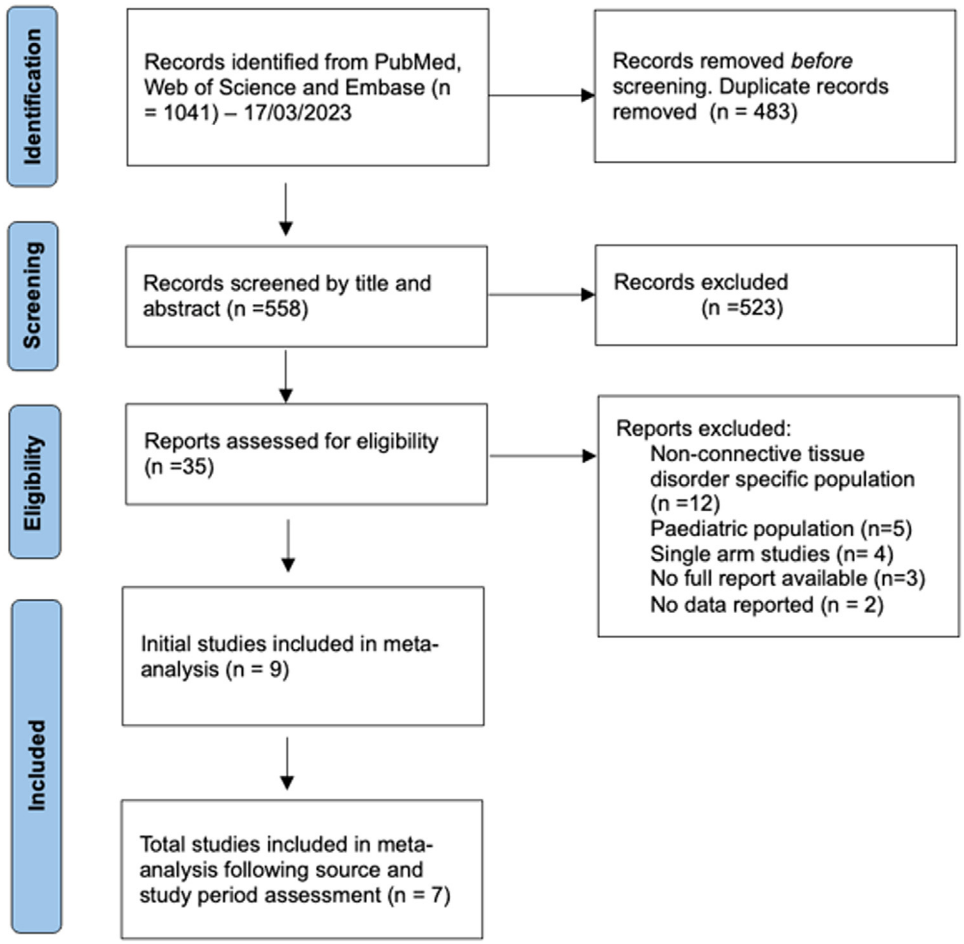

Figure 1. PRISMA flowchart. Systematic Review and Meta-Analysis (PRISMA) illustration of study selection.

10.5 years. The pooled reimplantation group demonstrated a mortality incidence of 5.9% compared with 6.5% of patients who received remodeling VSARR (OR 0.66, 95% CI 0.30 to 1.48, I^2 = 30%, p = 0.32). Postoperative mortality did not achieve statistical significance between the patient intervention groups. However, in the sensitivity analysis, the exclusion of patients who received annuloplasty in addition to remodeling surgery (EMFU 10.9 years, 257 patients) led to an incidence of 7.5% mortality (OR 0.19, 95% CI 0.06 to 0.64, I^2 = 0%, p = 0.007). Pooling demonstrated postoperative survival in the reimplantation group to be superior to remodeling surgery without additional structural annuloplasty.

The rates of reoperation, with an EMFU of 10.3 years, were reported in an accumulative 449 patients with an incidence of 8.1% in the implantation group and 8.9% in the remodeling intervention group (OR 0.35, 95% CI 0.04 to 3.30, I^2 = 81%, p = 0.36). The sensitivity analysis excluding studies and subgroups of patients that received remodeling with annuloplasty VSARR (EMFU 10.6 years) demonstrated a reoperation incidence of 10.0% in the reimplantation group and 13.0% in the remodeling group (OR 0.43, 95% CI 0.05 to 3.53, I^2 = 71%, p = 0.43) (Figure 2). The meta-analysis of included studies did not reach statistical significance in the reoperation rate between reimplantation

Table 1
Studies included

Study	Year of Publication	Type of Study	Study Period	Newcastle-Ottawa Scale	Reimplantation	Remodelling	Remodelling + annuloplasty (%)
Bethea, et al. [18]	2004	Retrospective Cohort Study	1994-2002	7	7	58	0.00
Chavette, et al. [19]	2022	Multi-Centre Retrospective Cohort Study	1996-2018	6	100	137	79.70
Elbatarny, et al. [17]	2023	Retrospective Cohort Study	1988-2008	9	43	24	29.00
Patel, et al. [20]	2008	Retrospective Cohort Study	1996-2006	7	44	40	0.00
Price, et al. [21]	2015	Retrospective Cohort Study	1997-2013	7	69	29	0.00
Schoenhoff, et al. [22]	2015	Retrospective Cohort Study	1995-2014	7	24	5	0.00
Wang, et al. [23]	2010	Retrospective Cohort Study	2003-2007	6	9	8	0.00

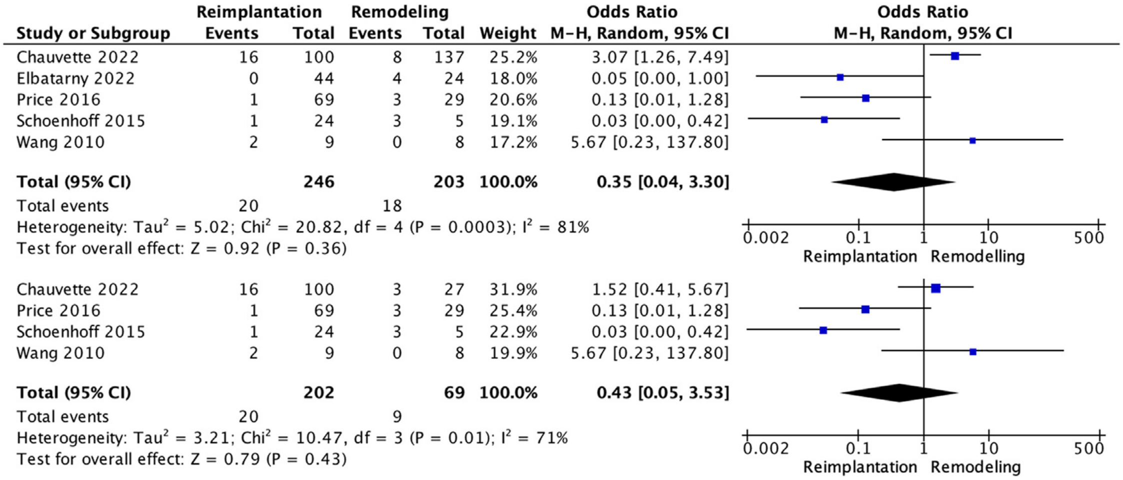

Figure 2. Rates of reoperation forest plot. Meta-analysis of data from included studies on rates of reoperation and sensitivity analysis, excluding studies and patient subgroups that received annuloplasties in addition to remodeling.

and remodeling VSARR, regardless of the addition of structural annuloplasty in remodeling surgery.

The occurrence of moderate to severe postoperative aortic regurgitation in 402 patients with an EMFU of 10.9 years was recorded as 8.8% and 16.3% in patients who received reimplantation and remodeling VSARR (OR 0.56, 95% CI 0.31 to 1.02, $I^2 = 47\%$, p = 0.06, respectively). The sensitivity analysis excluding patients who received annuloplasty in addition to remodeling surgery with an EMFU of 11.4 years demonstrated an occurrence of 10.1% in the reimplantation and 25.3% in the remodeling group (OR 0.23, 95% CI 0.10 to 0.53, $I^2 = 47\%$, p = 0.0005, respectively) (Figure 3). Therefore, the sensitivity analysis demonstrates that patients with CTDs who received remodeling surgery in the absence of annuloplasty are significantly more likely to develop aortic insufficiency.

Discussion

Patients with CTDs are diagnosed earlier in life as a result of improved genetic testing and undergo repeated multi-imaging surveillance of aortic function and diameter. In addition to medical management of blood pressure, offering prophylactic aortic root replacement is well established within the practice.[24,25] Although the indication for prophylactic surgery alters between associated CTDs, the broad movement toward valve-sparing surgery considers clinical evidence and the burden of anticoagulation/reoperation in mechanical/bioprosthetic valves on the patient's quality of life.[26,27] The use of prophylactic surgery in concordance with the young age of presenting patients with CTD provides a long-expected postoperative life expectancy. Therefore, this begs the question of whether preserving the native valve in VSARR provides the long-term durability necessary in patients with CTDs. In a 2022 study, Svensson et al[28] propensity matched and compared the long-term outcomes of reimplantation-only VSARR in 214 patients with CTDs against 645 patients without. The 10-year follow-up reported no difference in reoperation, mortality, or aortic regurgitation rates between the study groups, demonstrating the structural integrity of the valves of patients with CTDs. The study excluded remodeling techniques because of perceived postoperative failure; however, with the starting study year of 1980, it is noted that

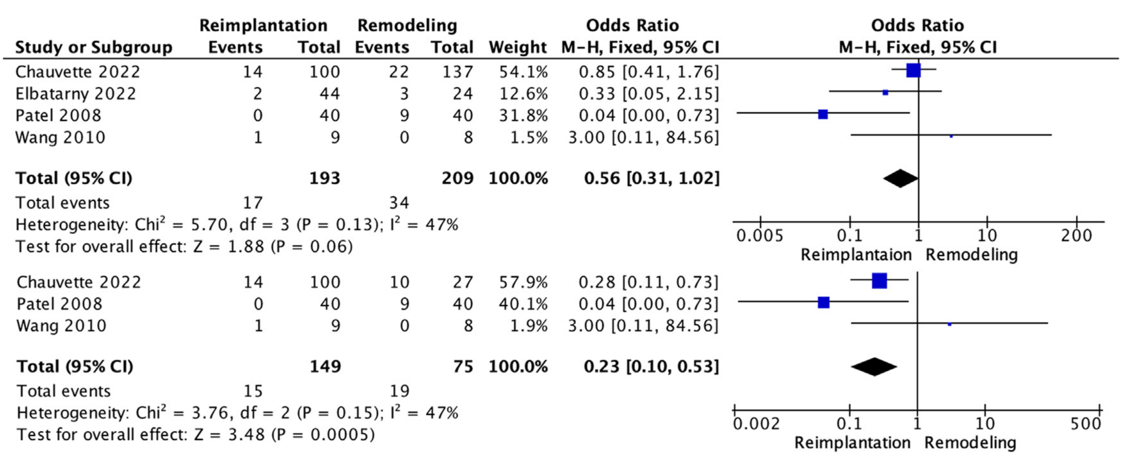

Figure 3. Rates of aortic regurgitation forest plot. Meta-analysis data from included studies on the occurrence of aortic regurgitation and sensitivity analysis, excluding studies and patient subgroups that received annuloplasties in addition to remodeling.

Table 2
Demographics

		Bethea, et al. [18]	Chavette, et al. [19]	Elbatarny, et al. [17]	Patel, et al. [20]	Price, et al. [21]	Schoenhoff, et al. [22]	Wang, et al. [23]
	Reimplantation (n)	7	100	43	44	69	24	9
	Remodelling (n)	58	137	24	40	29	5	8
Age (Mean)	Reimplantation	33.6*	35	39	29.2	36	27	28
	Remodelling		36.6*	40				
Male Gender (%)	Reimplantation	72.3	70	64	72.6	72.5		55
	Remodelling		64.5	62				
Connective Tissue Disorders (%)	Marfan's Syndrome	67.7	82.4	100	100	100	100	100
	Ehlers-Danlos Syndrome	4.6	1.3	0	0	0	0	0
	Loeys-Dietz Syndrome	0	5.9	0	0	0	0	0
	Other	27.7	10.5	0	0	0	0	0
Mean Aortic Root Diameter (mm)	Reimplantation		50		51	50.0†	48	55
	Remodelling		52.4*					
Aortic Regurgitation ≥2 (%)	Reimplantation	35.4	37	91		14.4	14	35
	Remodelling		43.5	88				
Bicuspid Aortic Valve (%)	Reimplantation		3		1.2	2.2		0
	Remodelling		8					
Aortic Dissection (Acute/Chronic) (%)	Reimplantation		10	9	12.5	4.1		15
	Remodelling		5.1	16				
Concomitant Cardiac Surgery (%)	Reimplantation	6.2	29	34.9	46.4	53.1	6.9	25
	Remodelling		26.8	41.7				
NYHA Functional Class ≥3 (%)	Reimplantation			9		8.2		15
	Remodelling			12				

* Estimated value.
† Median value.

remodeling developments with structural annuloplasty had not yet been implemented.[28] Given the durability of the aortic valve after surgery, postoperative aortic regurgitation is attributed to annular dilation secondary to CTD vasculopathy; intraoperative repair of the aortic cusps is, at times, required to rectify pathology resulting from prolonged preoperative annular dilation.[29]

During reimplantation, the native valve is sutured into the Dacron graft, protecting the reimplanted valve from dilation, as opposed to remodeling surgery in which the vascular graft is sutured into the remaining aortic wall above the insertion of valve leaflets, thereby providing minimal structural support against later annular dilation. Subsequently, the development of remodeling techniques used suture and ring extra-aortic structural annuloplasty to avoid redilation of the aortic annulus and postoperative aortic regurgitation by way of the stabilization of the atrioventricular junction.[25,30] The clinical significance of additional structural support in remodeling surgery is evidenced in our meta-analysis; although the midterm rates of postoperative aortic regurgitation and mortality were not significant between the study groups, after sensitivity analysis and the exclusion of patients who underwent remodeling and annuloplasty, the outcomes favored reimplantation surgery. Although this meta-analysis does not assess the patient's cause of death, there may be an association of postoperative aortic regurgitation (in the absence of basal annuloplasty) and mortality because of the development of heart failure. The current body of knowledge does not allow the subgrouping of remodeling with annuloplasty alone versus reimplantation clinical outcomes. Previous studies suggest that surgeon and institution experience influences the occurrence of postoperative aortic regurgitation and requirement of reoperation, with high-volume centers reporting 10-year freedom from reoperation >90% in patients with Marfan syndrome.[31] This may be explained by the more rigorous correction of the aortic valve, measuring the effective height and optimal cusp free margin alignment to avoid prolapse and later aortic regurgitation secondary to the reduction in aortic root diameter.[32,33]

Previous techniques and clinical outcomes, primarily annular dilation, have led to an increased favoring of reimplantation VSARR in patients with CTDs, despite the consideration of postoperative hemodynamics. A Swiss study compared the fluid dynamic composition of postoperative structures after reimplantation and remodeling surgery in porcine research subjects. The results demonstrated an increased duration of high pressure (>150 mm Hg) and low shear stress in reimplantation surgery, as opposed to remodeling surgery, that produced hemodynamic models more comparable with the native root structures.[34] The poor hemodynamic results may be associated with the use of straight tube grafts in reimplantation VSARR, whereas remodeling techniques preserve the sinuses of Valsalva. The introduction of bulb-shaped neo-Valsalva grafts in reimplantation surgery has produced satisfactory Valsalva to aortoventricular junction ratios, generating geometry more akin to natural physiology and improved valve durability.[35,36] The assessment of reimplantation with neo-Valsalva grafts and remodeling with extra-aortic annuloplasty demonstrated similar hemodynamic results in multiple studies. The heterogeneity of human and porcine anatomic structures should be considered in view of the aforementioned studies.[37] Real-world long-term patient data continue to report excellent results of reimplantation surgery using neo-Valsalva grafts.[38]

Although patients with CTDs continue to be at a high risk of distal aortic dissection after root surgery and require life-long follow-up and assessment of aortic function, prophylactic VSARR continues to evidence improved long-term clinical outcomes.[39] Given the complexity of VSARR surgery, the impact of surgeon preference and experience on patient outcomes should not be underestimated.[40] Our analysis has demonstrated that remodeling without basal annuloplasty is not advisable in patients with CTDs. We believe this analysis provides the highest quality available data specific to patients of this demographic and warrants further research of CTD-specific VSARR outcomes given refined surgical techniques. Randomization, control of covariables, and prospective studies are essential to the improved validity of future research endeavors in this field.

Limitations

This meta-analysis has several limitations, including the limited study size included in the analysis. The occurrence of thromboembolic events and early outcomes, including the incidence of in-hospital mortality, stroke, and returning to theater for active bleeding, were reported by a significant number of studies to allow pooling. However, the infrequency of events in the context of low patient quantities did not allow meaningful analysis. In addition, the limited number of included studies resulted in a low-quality assessment of funnel plots and the possibility of reporting/publication bias.

Because of the nature of VSARR surgery in patients of this limited etiology, there is a lack of randomized data and statistical adjustment to treat for bias selection, with only 1 of the included studies using propensity score matching. The sensitivity analysis by way of nonbias-treated data from the study by David et al[16] (excluding the study by Elbatarny et al[17]) only altered the statistical significance of long-term aortic regurgitation.

Several of the included studies produced subgroup data comparing reimplantation and remodeling surgery under the larger study group of VSARR. Subsequently, not all demographic data are available specific to our study groups (Table 2).

Conclusions

Remodeling techniques have demonstrated comparable midterm clinical outcomes in patients with CTDs compared with reimplantation VSARR surgery. The exclusion of patients who received structural annuloplasty produced superior rates of mortality and aortic regurgitation in the reimplantation study group. There may be postoperative physiologic advantages provided by remodeling surgery, and more research is required to assess the long-term effects of structural annuloplasty and remodeling surgery in patients of this demographic.

Declaration of Competing Interest

The authors have no competing interest to declare.

Author Contributions

Conceptualization: Samuel Burton. Data curation: Samuel Burton. Formal analysis: Samuel Burton. Investigation: Samuel Burton, Alexander Reynolds. Method: Samuel Burton, Alexander Reynolds, and Nicola King. Project administration: Samuel Burton. Software: Alexander Reynolds and Samuel Burton. Supervision: Sanjay Asopa and Amit Modi. Validation: Nicola King. Visualization: Samuel Burton. Writing − original draft: Samuel Burton. Writing − review & editing: Samuel Burton, Alexander Reynolds, Nicola King, Sanjay Asopa, and Amit Modi.

Data Availability

The data underlying this article is available in the article and in its attached supplementary material.

This research has been accepted for presentation at the European Association of Cardio-Thoracic Surgery 2023 Annual meeting in Vienna. This review is not currently registered.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2023.11.066.

1. Grygiel-Górniak B, Oduah MT, Olagunju A, Klokner M. Disorders of the aorta and aortic valve in connective tissue diseases. *Curr Cardiol Rep* 2020;22:70.
2. Pizano A, Tenorio ER, Tanaka A, Oderich GS. Chapter 24. Aneurysmatic degeneration of connective tissue diseases: from diagnosis to treatment. In: Settembrini P, Settembrini AM, eds. Vascular Surgery. Cambridge: Academic Press; 2022:273–295.
3. Zeigler SM, Sloan B, Jones JA. Pathophysiology and pathogenesis of Marfan syndrome. In: Halper J, ed. Progress in Heritable Soft Connective Tissue Diseases. Cham: Springer International Publishing; 2021:185–206.
4. Flynn CD, Tian DH, Wilson-Smith A, David T, Matalanis G, Misfeld M, Mastrobuoni S, El Khoury G, Yan TD. Systematic review and meta-analysis of surgical outcomes in Marfan patients undergoing aortic root surgery by composite-valve graft or valve sparing root replacement. *Ann Cardiothorac Surg* 2017;6:570–581.
5. Soto ME, Ochoa-Hein E, Anaya-Ayala JE, Ayala-Picazo M, Koretzky SG. 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. *J Thorac Dis* 2021;13:4830–4844.
6. Pepper J. External aortic support and other alternative strategies in the management of aortic pathology of patients with connective tissue disorders. In: Sellke FW, Coselli JS, Sundt TM, Bavaria JE, Sodha NR, eds. Aortic Dissection and Acute Aortic Syndromes. Cham: Springer International Publishing; 2021:469–482.
7. Choudhary SK, Goyal A. Aortic root surgery in Marfan syndrome. *Indian J Thorac Cardiovasc Surg* 2019;35(suppl 2):79–86.
8. David TE, Feindel CM. An aortic valve-sparing operation for patients with aortic incompetence and aneurysm of the ascending aorta. *J Thorac Cardiovasc Surg* 1992;103:617–621. discussion 622.
9. Sarsam MA, Yacoub M. Remodeling of the aortic valve anulus. *J Thorac Cardiovasc Surg* 1993;105:435–438.
10. Klotz S, Stock S, Sievers HH, Diwoky M, Petersen M, Stierle U, Richardt D. Survival and reoperation pattern after 20 years of experience with aortic valve-sparing root replacement in patients with tricuspid and bicuspid valves. *J Thorac Cardiovasc Surg* 2018;155:1403–1411.e1.
11. Zhou Z, Liang M, Huang S, Wu Z. Reimplantation versus remodeling in valve-sparing surgery for aortic root aneurysms: a meta-analysis. *J Thorac Dis* 2020;12:4742–4753.
12. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71.
13. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010;25:603–605.
14. Sterne JAC, Sutton AJ, Ioannidis JPA, Terrin N, Jones DR, Lau J, Carpenter J, Rücker G, Harbord RM, Schmid CH, Tetzlaff J, Deeks JJ, Peters J, Macaskill P, Schwarzer G, Duval S, Altman DG, Moher D, Higgins JPT. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ* 2011;343:d4002.
15. Review Manager (RevMan) [computer program]. version 5.4. London: The Cochrane Collaboration; 2020.
16. David TE, Park J, Tatangelo M, Steve Fan CP, Ouzounian M. Cardiovascular events after aortic root repair in patients with Marfan syndrome. *J Am Coll Cardiol* 2023;82:1068–1076.
17. Elbatarny M, David TE, David CM, Chung JCY, Lafreniere-Roula M, Ouzounian M. Improved outcomes of reimplantation vs remodeling in Marfan syndrome: a propensity-matched study. *Ann Thorac Surg* 2023;115:576–582.
18. Bethea BT, Fitton TP, Alejo DE, Barreiro CJ, Cattaneo SM, Dietz HC, Spevak PJ, Lima JAC, Gott VL, Cameron DE. Results of aortic valve-sparing operations: experience with remodeling and reimplantation procedures in 65 patients. *Ann Thorac Surg* 2004;78(3):767–772. discussion 767.
19. Chauvette V, Kluin J, de Kerchove L, El Khoury G, Schäfers HJ, Lansac E, El-Hamamsy I. Outcomes of valve-sparing surgery in heritable aortic disorders: results from the AVIATOR registry. *Eur J Cardiothorac Surg* 2022;62:ezac366.
20. Patel ND, Weiss ES, Alejo DE, Nwakanma LU, Williams JA, Dietz HC, Spevak PJ, Gott VL, Vricella LA, Cameron DE. Aortic root operations for Marfan syndrome: a comparison of the Bentall and valve-sparing procedures. *Ann Thorac Surg* 2008;85:2003–2010. discussion 2010.
21. Price J, Magruder JT, Young A, Grimm JC, Patel ND, Alejo D, Dietz HC, Vricella LA, Cameron DE. Long-term outcomes of aortic root operations for Marfan syndrome: a comparison of Bentall versus aortic valve-sparing procedures. *J Thorac Cardiovasc Surg* 2016;151:330–336.
22. Schoenhoff FS, Langhammer B, Wustmann K, Reineke D, Kadner A, Carrel T. Decision-making in aortic root surgery in Marfan syndrome: bleeding, thromboembolism and risk of reintervention after valve-sparing or mechanical aortic root replacement. *Eur J Cardiothorac Surg* 2015;48:931–935. discussion 35−36.
23. Wang R, Ma WG, Tian LX, Sun LZ, Chang Q. Valve-sparing operation for aortic root aneurysm in patients with Marfan syndrome. *Thorac Cardiovasc Surg* 2010;58:76–80.
24. van Elsäcker E, Vink AS, Menke LA, Pals G, Bokenkamp R, Backx ACPM, Hilhorst-Hofstee Y, Blom NA, Van der Hulst AE. Growth of the aortic root in children and young adults with Marfan syndrome. *Open Heart* 2022;9:e002097.
25. Bombardieri E, Rohrbach M, Greutmann M, Matyas G, Weber R, Radulovic J, Fasnacht-Boillat M, Linka A, De Pasquale G, Bonassin F, Attenhofer Jost CH. Marfan syndrome and related connective tissue disorders in the current era in Switzerland in 103 patients: medical and surgical management and impact of genetic testing. *Swiss Med Wkly* 2020;150:w20189.
26. Sá MP, Jacquemyn X, Van den Eynde J, Chu D, Serna-Gallegos D, Coselli JS, Sultan I. Long-term outcomes of valve-sparing aortic root versus composite aortic valve graft replacement for aortic root

aneurysm: meta-analysis of reconstructed time-to-event data. *Am J Surg* 2023;226:371–378.
27. Treasure T, King A, Hidalgo Lemp L, Golesworthy T, Pepper J, Takkenberg JJ. Developing a shared decision support framework for aortic root surgery in Marfan syndrome. *Heart* 2018;104:480–486.
28. Svensson LG, Vargo PR, Desai MY, Kalahasti V, Griffin B, Roselli EE, Rosinski BF, Rajeswaran J, Blackstone EH. Aortic valve reimplantation in patients with connective tissue disorders: are the leaflets durable? *J Thorac Cardiovasc Surg* 2023;166:1617–1626.e6.
29. Ram E, Lau C, Dimagli A, Chu NQ, Soletti G, Gaudino M, Girardi LN. Long-term durability of valve-sparing root replacement in patients with and without connective tissue disease [published May 6, 2023]. *J Thorac Cardiovasc Surg* 10.1016/j.jtcvs.2023.04.033.
30. Lenoir M, Maesen B, Stevens LM, Cartier R, Demers P, Poirier N, Tousch M. El-Hamamsy I. Reimplantation versus remodelling with ring annuloplasty: comparison of mid-term outcomes after valve-sparing aortic root replacement. *Eur J Cardiothorac Surg* 2018;54:48–54.
31. David TE, David CM, Manlhiot C, Colman J, Crean AM, Bradley T. Outcomes of aortic valve-sparing operations in Marfan syndrome. *J Am Coll Cardiol* 2015;66:1445–1453.
32. Youssefi P, El-Hamamsy I, Lansac E. Rationale for aortic annuloplasty to standardise aortic valve repair. *Ann Cardiothorac Surg* 2019;8:322–330.
33. Schneider U, Ehrlich T, Karliova I, Giebels C, Schäfers HJ. Valve-sparing aortic root replacement in patients with Marfan syndrome—the Homburg experience. *Ann Cardiothorac Surg* 2017;6:697–703.
34. Berdajs D, Mosbahi S, Strano F, Forro Z, Burki M, von Segesser LK. Impact of synthetic elements on aortic root haemodynamics: computed fluid dynamics of aortic root reconstruction and valve reimplantation. *Eur J Cardiothorac Surg* 2017;51:432–441.
35. Sasaki K, Kunihara T, Kasegawa H, Seki M, Seki H, Takada J, Sasuga S, Kumazawa R, Umezu M, Iwasaki K. Aortic root geometry following valve-sparing root replacement with reimplantation or remodeling: experimental investigation under static continuous pressure. *J Artif Organs* 2021;24:245–253.
36. Oechtering TH, Hons CF, Sieren M, Hunold P, Hennemuth A, Huellebrand M, Drexl J, Scharfschwerdt M, Richardt D, Sievers HH, Barkhausen FA. Time-resolved 3-dimensional magnetic resonance phase contrast imaging (4D Flow MRI) analysis of hemodynamics in valve-sparing aortic root repair with an anatomically shaped sinus prosthesis. *J Thorac Cardiovasc Surg* 2016;152:418–427.e1.
37. Seki M, Kunihara T, Takada J, Sasaki K, Kumazawa R, Seki H, Sasuga S, Fukuda H, Umezu M, Iwasaki K. Comparison of hemodynamics and root configurations between remodeling and reimplantation methods for valve-sparing aortic root replacement: a pulsatile flow study. *Surg Today* 2023;53:845–854.
38. Chirichilli I, Scaffa R, Irace FG, Salica A, Weltert LP, D'Aleo S, Chiariello L, De Paulis RD. Twenty-year experience of aortic valve reimplantation using the valsalva graft. *Eur J Cardiothorac Surg* 2023;63:ezac591.
39. Forteza Gil A, Martinez-Lopez D, Centeno J, Rivas Oyarzabal J, García Suarez J, de Villarreal Soto JE, Rosado ECR, Vera Puente B, Villar García S, Ospina Mosquera VM, Mingo S, Moñivas V, Serrano-Fiz S, Martínez López D. Aortic valve reimplantation in patients with connective tissue syndromes: a 15-year follow-up. *Eur J Cardiothorac Surg* 2022;62:ezac149.
40. Patlolla SH, Saran N, Dearani JA, Stulak JM, Schaff HV, Greason KL, Daly RC, King KS, Pochettino AB. Outcomes and risk factors of late failure of valve-sparing aortic root replacement. *J Thorac Cardiovasc Surg* 2022;164:493–501.e1.