Systematic Review

Valve-sparing aortic root replacement using the reimplantation (David) technique: a systematic review and meta-analysis on survival and clinical outcome

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Background: Current guidelines recommend valve-sparing aortic root replacement (VSRR) procedures over valve replacement for the treatment of root aneurysm. The reimplantation technique seems to be the most widely used valve-sparing technique, with excellent outcomes in mostly single-center studies. The aim of this systematic review and meta-analysis is to present a comprehensive overview of clinical outcomes after VSRR with the reimplantation technique, and potential differences for bicuspid aortic valve (BAV) phenotype.

Methods: We conducted a systematic literature search of papers reporting outcomes after VSRR that were published since 2010. Studies solely reporting on acute aortic syndromes or congenital patients were excluded. Baseline characteristics were summarized using sample size weighting. Late outcomes were pooled using inverse variance weighting. Pooled Kaplan-Meier (KM) curves for time-to-event outcomes were generated. Further, a microsimulation model was developed to estimate life expectancy and risks of valve-related morbidity after surgery.

Results: Forty-four studies, with 7,878 patients, matched the inclusion criteria and were included for analysis. Mean age at operation was 50 years and almost 80% of patients were male. Pooled early mortality was 1.6% and the most common perioperative complication was chest re-exploration for bleeding (5.4%). Mean follow-up was 4.8±2.8 years. Linearized occurrence rates for aortic valve (AV) related complications such as endocarditis and stroke were below 0.3% patient-year. Overall survival was 99% and 89% at 1- and 10-year respectively. Freedom from reoperation was 99% and 91% after 1 and 10 years, respectively, with no difference between tricuspid and BAVs.

Conclusions: This systematic review and meta-analysis shows excellent short- and long-term results of valve-sparing root replacement with the reimplantation technique in terms of survival, freedom from reoperation, and valve related complications with no difference between tricuspid and BAVs.

Keywords: Valve-sparing operations; reimplantation technique; meta-analysis

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Introduction

Valve-sparing aortic root replacement (VSRR) procedures have progressively gained ground in the surgical treatment of aortic root aneurysms with or without aortic regurgitation. Recent comprehensive reports have shown superior outcomes in VSRR compared to composite valve-graft conduit aortic root replacement (i.e., the Bentall or the so called "Bio-Bentall" procedure) in terms of valve-related complications, but also better survival after VSRR is observed (1). In the current American as well as European guidelines on the management of aortic disease, valve-sparing is preferred over valve replacement, especially in younger patients and when performed in experienced centers. However, there are no specific recommendations regarding the type of valve-sparing procedure (2,3). Several valve-sparing techniques have been developed over the years, of which the remodeling technique (Yacoub) and the reimplantation technique (David) are the most renowned and employed (4,5). The reimplantation technique seems to be the most widely applied valve-sparing technique, according to the literature, with excellent outcomes (6). Excellent clinical outcome has been reported in patients after VSRR with the reimplantation both in bicuspid and tricuspid aortic valve (TAV) phenotypes (7), however, these are mostly single-center studies. Previous meta-analysis either have analyzed the results of both reimplantation and remodeling techniques altogether (6,8) or have focused on studies comparing VSRR (regardless of technique) with the Bentall procedure (9,10). The aim of this systematic review and meta-analysis is to present a comprehensive overview of survival, reoperation rate and valve-related clinical outcomes after the VSRR, using solely the reimplantation technique, and to investigate potential differences in outcomes for bicuspid aortic valve (BAV) phenotype.

Methods

Search strategy

To establish an overview of reported outcomes, this systematic literature search was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (11). On October 1st, 2022, Embase, Medline, Web of Science, Cochrane, and Google Scholar were searched by a biomedical information specialist (search terms are available in Appendix 1). The search was limited to studies that were published after January 1st, 2010, in order, on the one hand to capture the latest report of large and older series and, on the other hand, to capture more recent series that used the latest and current evolution of the reimplantation technique. Four researchers (P.J.G, S.S, L.Z and A.S.) independently reviewed abstracts and full texts. All studies that reported on outcomes after VSRR, utilizing only the reimplantation technique, with a sample size ≥30 patients and were published in English were included. Studies solely reporting on acute aortic syndrome or congenital patients were excluded. In case of multiple publications on overlapping study populations, the publication with the greatest total follow-up in patient-years and/or overall completeness of data was included for each outcome of interest, separately. In case of disagreement, an agreement was negotiated.

Data extraction

Microsoft Office Excel 2011 (Microsoft Corp., Redmond, WA, USA) was used for data extraction. In case the total follow-up in patient-years was not reported, it was calculated by multiplying the number of patients with the mean follow-up (or median follow-up, when the mean was not provided). Outcomes were recorded according to the 2008 Society of Thoracic Surgeons/American Association for Thoracic Surgery/European Association for Cardio-Thoracic Surgery guidelines (12). Early mortality was defined as either hospital mortality or 30-day mortality. Early reoperation was defined as reoperation on the aortic valve (AV) during the index hospitalization. A sensitivity analysis was performed for studies reporting 30-day mortality.

Statistical analyses

Continuous variables are presented as mean ± standard deviation (SD). Categorical variables are presented as counts and percentages. Linearized occurrence rates of events are presented as percentages per year and were calculated by dividing the number of reported events in a study by the total number of patient-years of follow-up for that study. Baseline characteristics were summarized using sample size weighting. Late outcome was pooled using inverse variance weighting. The estimation of between-study variance was performed according to the DerSimonian and Laird method in a random-effects model (13). In case an event did not occur in a cohort of patients, it was assumed that 0.5 patients in this cohort experienced the event for pooling purposes (continuity correction). P values of <0.05 were considered statistically significant. The Cochran-Q statistic and I^2 statistic were used to assess the proportion of total heterogeneity for an outcome attributable to between-study heterogeneity. Statistical sources of heterogeneity in outcomes with at least substantial heterogeneity (I^2>60%) were explored by means of univariable meta-regression. Sensitivity analyses was done by temporarily excluding studies with lower sample size (or patient years in case of late outcome).

Kaplan-Meier (KM) meta-analysis

Reconstructed estimates of individual patient time-to-event data (IPD), derived from published KM curves, were extracted and combined using the method described by Guyot *et al.* (14). First, the published KM curves for the outcome of interest were digitized. Second, the estimated time-to-event data of all individual patients were extracted from this digitized curve. The assumption of a linear censorship rate between each time point at which the remaining number of patients still at risk were specified was made. Lastly, the reconstructed IPD of each individual study were combined for each time-to-event outcome, to generate pooled KM curves.

Microsimulation

A microsimulation model based on the pooled early and late outcome estimates of our meta-analysis was developed to estimate life expectancy and risks of valve-related morbidity after surgery. The health states assumed in the model were alive and dead. The parameters of the models are shown in Table S1. Transition probabilities between health state were based on background mortality, mortality due to valve-related events (AV reintervention, endocarditis, stroke, thrombo-embolism, bleeding, valve-thrombosis), and excess mortality. Excess mortality is expressed as risk ratio in a certain timeframe, estimated by multiplying background mortality + mortality due to valve related events with a risk ratio to match observed mortality derived from the meta-analysis (Figure S1). Details on obtaining matched background mortality, estimating excess mortality, and time-specific risk ratios are presented in Appendix 2 and Tables S2,S3. The occurrence of AV reintervention not due to valve thrombosis and endocarditis was modelled according to the flexible parametric survival model that fitted the time-to-event data of each time-to-event outcome best. In case of BAV subgroup there was not enough KM data for these models to converge, so the linearized occurrence rate was used (Table S4). Probabilistic sensitivity analysis (PSA) was performed to consider the uncertainty in input parameters of the microsimulation and to reflect its implications for uncertainty in outcomes for all subgroups. During PSA, the model considered a sample size of 1,000 patients per set and ran for 1,000 different sets of randomly drawn input parameters based on their respective distributions. Details are presented in Appendix 2. Internal validation of late survival and AV-reintervention was assessed by plotting microsimulation events and observed events of KM analysis from the meta-analysis. R (version 4.0.2) and statistical packages meta, survival, darthtools, dampack were used to perform the analysis.

Results

The literature search resulted in 1,571 publications. The selection procedure of this systematic review is shown in *Figure 1*. A total number of 44 studies matched with the inclusion and exclusion criteria and were included for analysis, of which 11 publications separately reported (partially) outcomes on TAV (15-25) and 12 publications on BAV (7,17,20,21,25-32). The full list of studies included in this review is presented in the Supplementary material (Appendix 3). Detailed information of characteristics is presented in Table S5. A total of 7,878 patients were included with a pooled mean follow-up of 4.8±2.8 years. Pooled patient and procedural characteristics are presented in *Table 1*.

Clinical outcomes

Table 2 entails early and late outcomes. Heterogeneity was low to high across outcome measures. Meta-regression revealed age to be a source of statistical heterogeneity for re-exploration for bleeding and late mortality (Table S6). Sensitivity analysis did not expose great variations in pooled outcomes when studies with a sample size lower than 25th percentile were (temporarily) excluded (Table S7). Valve-related events like endocarditis, stroke and bleeding were very low during follow-up. No event of valve-thrombosis was reported.

Overall survival

In total, 39 studies reported overall late survival by means of a KM curve, encompassing 5,511 patients. *Figure 2* shows the pooled KM curve of the overall survival, which was 99%

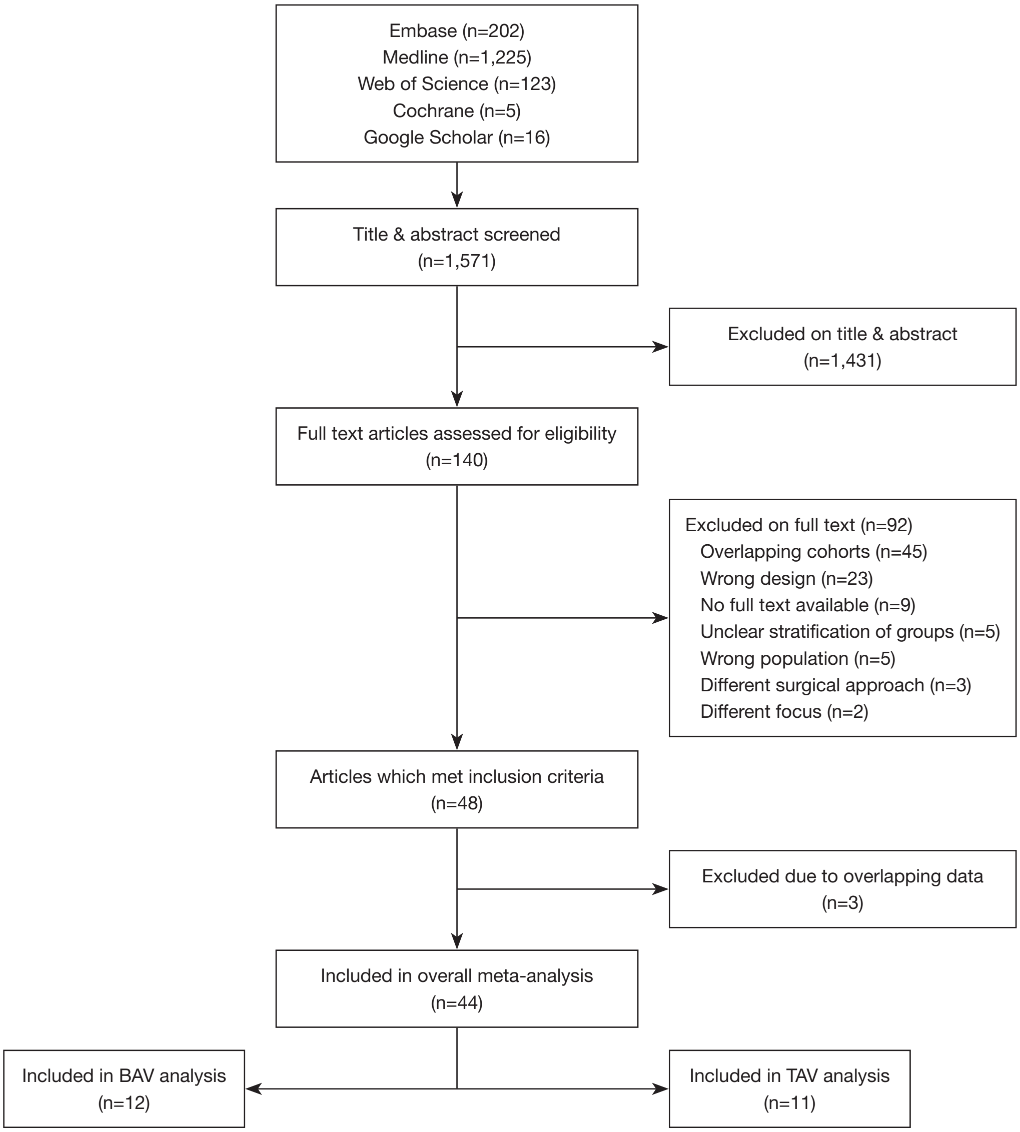

Figure 1 A flow chart of included studies. BAV, bicuspid aortic valve; TAV, tricuspid aortic valve. Note: 45 studies finally met the including criteria but 2 studies reported on the same cohort, therefore 44 cohort were finally used for analysis.

at 1-year and 89% at 10-year follow-up.

Freedom from reoperation

In 39 studies reporting freedom from late reoperation on the AV by means of a KM curve, 2,573 patients were available for pooled KM curves. *Figure 3* shows the pooled freedom from reoperation KM curve, which was 99% after 1 year and 91% at 10-year follow-up. Reoperation mortality was low (0.14% 95% CI: 0.08–0.23%, reported in 21 studies), although these were relatively young patients.

TAV versus BAV

A total of 11 studies presented a KM curve reporting survival and reoperation in TAV and 12 studies presented KM curve for BAV. *Figure 4A* shows survival in TAV compared to BAV, although the TAV patients are on average 4.7 years older than BAV patients (mean age 48.6 *vs.* 43.9 years, respectively).

Figure 4B presents the pooled KM curves of freedom from reoperation on the AV in 333 patients with TAV compared to 125 patients with BAV and shows no difference

Table 1 Pooled baseline characteristics

Variable	Pooled data	Range	Included studies (n)	Included patients (n)
Total patient number (n)	7,878	38–677	44	7,878
Surgical period (years)	1989–2022		44	7,878
Age (years), mean ± SD	50.64±12.23	32.30–64.00	44	7,878
Gender, male (%)	79.26	56.90–95.45	44	7,878
Comorbidity				
Renal insufficiency (dialysis) (%)	7.07	0–46.50	20	3,351
LV dysfunction (EF <30%)	3.23	0–10.49	13	2,879
Hypertension (%)	51.01	7.64–79.49	36	6,618
Coronary artery disease (%)	14.12	0–32.61	23	4,916
Connective tissue disease (%)	20.92	0–100	38	6,697
Bicuspid aortic valve (%)	21.80	0–100	43	7,721
Prior cardiac operation (%)	4.60	0–16.17	27	5,766
Emergency surgery (%)	6.95	0–42.11	32	6,259
Re-exploration for bleeding (%)	5.28	0–15.38	40	7,257
Concomitant procedure (n)	3,478	0–426	42	7,499
Mitral valve repair (%)	5.72	0–24.84	40	7,269
Mitral valve replacement (%)	0.14	0–2.63	26	3,571
Tricuspid valve surgery (%)	6.68	0–81	26	4,414
CABG (%)	10.01	0–29.63	41	7,342
Hemiarch repair (%)	16.01	0–90.24	30	5,112
Arch repair (%)	9.72	0–72.09	35	7,489
Other (VSD repair, MAZE, etc.) (%)	8.59	0–67.06	34	5,539
Extracorporeal circulation time, min, mean ± SD	173.18±37.07	98.37–238	42	7,768
Aortic cross-clamping time min, mean ± SD	138.47±27.12	97–242	43	7,827

SD, standard deviation; LV, left ventricular; EF, ejection fraction; CABG, coronary artery bypass grafting; VSD, ventricular septal defect.

in reoperation risk during 9 years of follow-up. *Figure 5* represents the 12.5-year cumulative risk of valve-related outcomes in TAV and BAV based on microsimulation model. The microsimulation model was well calibrated to account for competing mortality (Figure S2).

Discussion

This systematic review and meta-analysis provides an overview of the contemporary published evidence on valve-sparing root replacement utilizing the reimplantation (David) technique. Moreover, it shows that excellent short- and long-term results in terms of survival and freedom from reoperation, and valve related complications can be achieved in patients with aortic root aneurysms and/or AV regurgitation. In addition, these desirable results are realizable not only for TAVs, but also for bicuspid valves. The latter is usually present in younger patients that may benefit even longer from low valve-related events and improved survival. Although, current evidence is heterogeneous and fragmented and unfortunately does not allow for further investigation of potential determinants of

Table 2 Pooled clinical outcomes

Outcome	Value (%)	95% CI	I^2 (%)	Studies included (n)
Early outcomes				
Early mortality	1.56[a]	1.24–1.96	18	44
Reintervention on the aortic valve	0.51[a]	0.35–0.76	0	34
Reexploration for bleeding	5.39[a]	4.39–6.61	71	41
Stroke	1.02[a]	0.73–1.43	29	35
Late outcomes (LOR)				
Late mortality	0.92[b]	0.73–1.15	70	39
Reintervention on the aortic valve	0.74[b]	0.61–0.90	53	39
Endocarditis	0.23[b]	0.17–0.32	38	34
Stroke	0.27[b]	0.19–0.39	27	27
Bleeding	0.17[b]	0.09–0.32	29	15

[a], risk; [b], patient-year. CI, confidence interval; LOR, linearized occurrence rate.

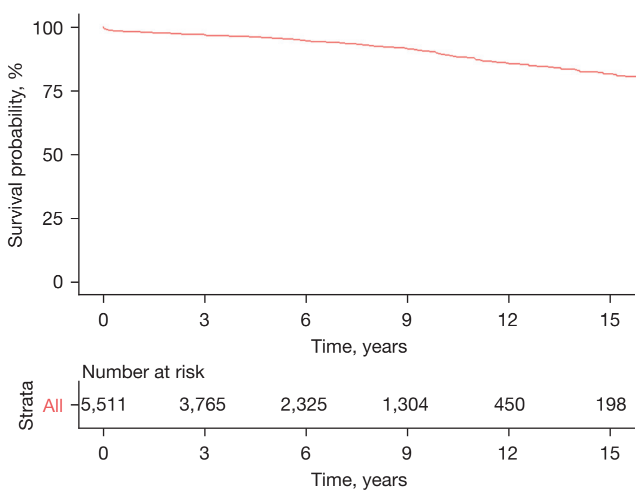

Figure 2 Pooled Kaplan-Meier curve of overall survival.

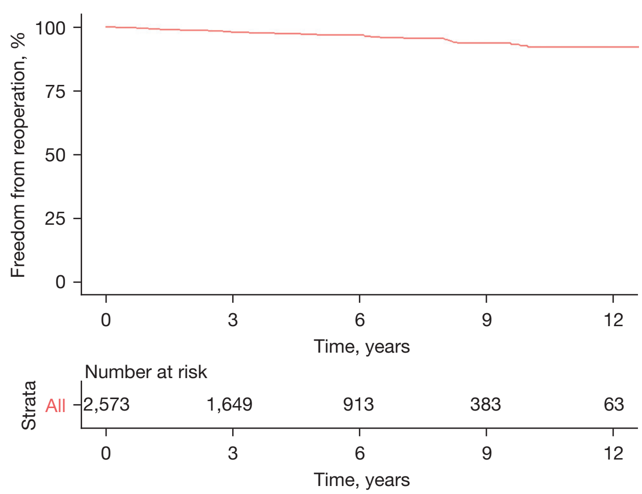

Figure 3 Pooled Kaplan-Meier curve overall freedom from reoperation on the aortic valve.

outcomes.

In patients presenting with isolated aneurysm of the aortic root, with a well-functioning AV, the most logical surgical approach would be replacement of the diseased aorta and preservation of the AV. However, in the 1960s, the early days of cardiac surgery, surgical techniques were not yet as advanced as to allow for valve-preserving techniques. Therefore, replacement of the entire AV/aortic root-complex with the Bentall/de Bono operation (33), a composite AV/root replacement, quickly gained popularity and was hence adopted as the early standard of care. With time however, the limitations of biologic and mechanical valve prostheses became increasingly evident, raising concerns over long-term results.

The early 1990s then introduced a paradigm shift in AV and root management for aortic root aneurysms. The remodeling and reimplantation technique, both, AV-sparing root replacement techniques, were introduced by Sir Magdi Yacoub and Tirone David, respectively (4,5). However, compared to the Bentall procedure, the reimplantation

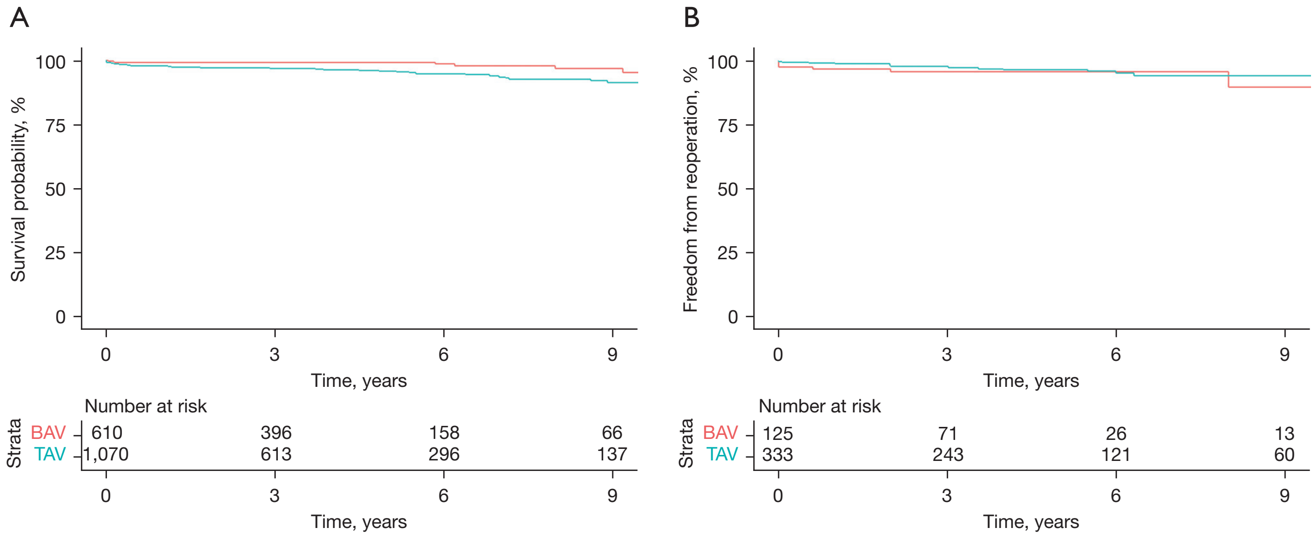

Figure 4 Pooled Kaplan-Meier curve of survival in TAV and BAV (A), and pooled freedom from reoperation on the aortic valve in TAV and BAV (B). BAV, bicuspid aortic valve; TAV, tricuspid aortic valve.

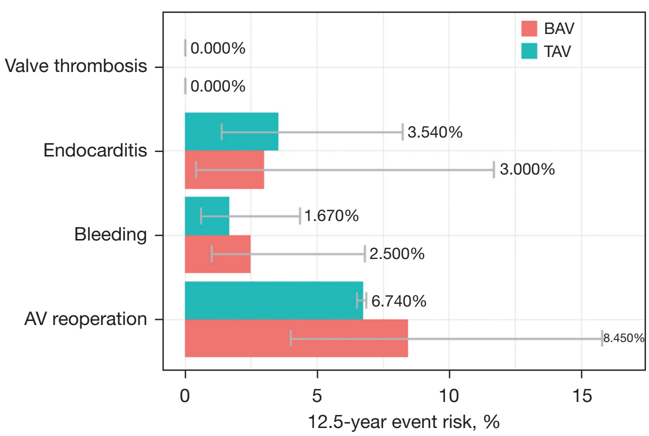

Figure 5 Cumulative 12.5-year risk of valve-related events for BAV and TAV based on microsimulation model. BAV, bicuspid aortic valve; TAV, tricuspid aortic valve.

technique is technically more demanding. Therefore, the complexity of the David procedures raised concerns and equally met with some resistance in the surgical community. Nonetheless, this procedure was initially employed in cases of a dilated root with a TAV, without significant valve regurgitation (34). The presence of a BAV or severe regurgitation were considered signs of leaflet disease that could potentially jeopardize valve durability and hence long-term results of the procedure.

The present meta-analysis demonstrates that the David operation is currently widely used with an increasing number of reports in the last 10 years. With increasing experience, the reimplantation technique has also been used in patients with BAVs. Although VSRR in BAV maybe more complex, especially in cases with an asymmetric configuration (35), however El Khoury and colleagues (36,37) demonstrated that repair of BAV with regurgitation is possible, provided that both the valve and the aortic root problems are treated simultaneously. Moreover, VSRR reimplantation has also been implemented in patients with connective tissue disease, such as Marfan syndrome (38), as well as in cases of acute Type-A aortic dissection (39,40). Furthermore, we have found that the reimplantation technique is nowadays often employed in the presence of root dilatation with severe regurgitation and is used in cases of severe aortic regurgitation without root aneurysm.

This meta-analysis of over 7,000 reported patients shows that the perioperative mortality is low at 1–2%, considering that on average there were 7% of emergency operations (usually for acute aortic dissection) and 4.6% of re-do cases. Further, the most frequent postoperative complication is surgical bleeding requiring chest re-exploration, with an incidence around 5%. During follow-up, valve-sparing procedures are associated with a very low incidence of valve-related complications. In particular, endocarditis and valve thromboembolism are very rarely reported. This is in line with a recently published, comprehensive propensity score matched study, comparing composite valve-graft replacements to valve-sparing root replacement (1), and in a similar study by Ouzounian *et al.* (41) that showed VSRR procedures were associated with reduced cardiac mortality and valve-related complications.

Long-term durability of the reimplanted valve, recurrence of regurgitation, and the risk of reoperation on the AV, have been the main concerns after introduction of this innovative approach. This meta-analysis, however, shows that the risk of reoperation on the AV is low in the long-term, with an incidence rate of 6–8% at 12-year follow-up based on microsimulation modeling. Nevertheless, the degree of preoperative AR is probably a predictor for AR recurrence, as well as the complexity of cusp repair (6,42). Cusp repair, particularly central cusp plication, has been increasingly used during the reimplantation technique. During reimplantation of the native valve into a graft, which is often smaller than the native dilated root, a mismatch between the length of the cusp free margin (which is elongated secondary to root dilatation) and the new root diameter can occur. Therefore, one or more cusps can be prolapsing despite a technically correct execution of valve reimplantation. In these cases, a central plication can easily remedy this problem. Surgeons have therefore become progressively more comfortable with such simple cusp repairs. However, a more complex repair, requiring decalcification or patch repair, are still associated with worse outcomes (42-44).

Limitations

It is noticeable that the included studies represent a heterogeneous population of patients, operated in different eras with possible different perioperative care. Additionally, the limited follow-up duration of the included studies does not allow for conclusions beyond the first postoperative decade. In addition, the pooled linearized occurrence rates are based on heterogeneous data, under the linearity assumption, and should be treated with considerable caution. The linearized occurrence rates for late complications are used as input for the microsimulation model, whereas these hazards may not be linear over time. In case of endocarditis, it is known that this hazard is higher shortly after surgery in patients operated because of AV endocarditis and stabilizes thereafter. Endocarditis rate was estimated in studies with short follow-up. Therefore, extrapolating this rate to the long-term may result in overestimation of lifetime endocarditis risk. We included only studies with cohorts greater than 30 patients; additionally, where available, we selected the largest series of published data from a center, hence selecting more experienced surgeons and centers. This may have led to some selection bias. Finally, since included articles were mainly retrospective studies, underreporting of events, in particular nonfatal events, is likely.

Conclusions

In conclusion, this meta-analysis demonstrates that valve-sparing reimplantation has excellent survival at 15 years after surgery, with a low risk of reoperation, for both TAV and BAV. Ultimately, the low incidence of valve-related complications such as thromboembolic or hemorrhagic events and infective endocarditis, translates into improved overall survival.

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Footnote

Conflicts of Interest: The authors declare no conflicts of interest.

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Supplementary

Appendix 1

Search terms

Embase

(aorta/exp OR 'aorta surgery'/de OR 'aorta reconstruction'/de OR aortoplasty/de OR 'aortic root surgery'/de OR 'aortic valve repair'/de OR 'aorta valve'/de OR 'aorta valve disease'/exp OR 'aorta disease'/exp OR 'aortic root aneurysm'/de OR (aort* OR Valsalva* OR root OR bav OR tav):ab,ti,kw) AND ('David operation'/de OR 'david procedure'/de OR 'aortic valve David reimplantation'/de OR 'aortic valve sparing procedure'/de OR 'valve sparing aortic root replacement'/de OR 'valve sparing root replacement'/de OR (((valve*) NEAR/6 (sparing* OR spare* OR preserv* OR reimplant*)) OR (david NEAR/3 (technique* OR surger* OR operat* OR procedure* OR reimplan* OR repair* OR intervention* OR tirone* OR resuspens*)) OR david-type OR david-i OR david-1 OR david-ii OR david-2 OR david-v OR david-5):ab,ti,kw OR (david):ti) NOT ([animals]/lim NOT [humans]/lim) NOT [conference abstract]/lim AND [english]/lim

Medline ALL Ovid

(exp Aorta / OR exp Aortic Diseases / OR aortic root aneurysm/ OR (aort* OR Valsalva* OR root OR bav OR tav).ab,ti,kw.) AND ((((valve*) ADJ6 (sparing* OR spare* OR preserv* OR reimplant*)) OR (david ADJ3 (technique* OR surger* OR operat* OR procedure* OR reimplan* OR repair* OR intervention* OR tirone* OR resuspens*)) OR david-type OR david-i OR david-1 OR david-ii OR david-2 OR david-v OR david-5).ab,ti,kw. OR (david).ti.) NOT (exp animals/ NOT humans/) AND english.la.

Cochrane

((aort* OR Valsalva* OR root OR bav OR tav):ab,ti) AND ((((valve*) NEAR/6 (sparing* OR spare* OR preserv* OR reimplant*)) OR (david NEAR/3 (technique* OR surger* OR operat* OR procedure* OR reimplan* OR repair* OR intervention* OR tirone* OR resuspens*)) OR david-type OR david-i OR david-1 OR david-ii OR david-2 OR david-v OR david-5):ab,ti OR (david):ti)

Web of science

TS=(((aort* OR Valsalva* OR root OR bav OR tav)) AND ((((valve*) NEAR/5 (sparing* OR spare* OR preserv* OR reimplant*)) OR (david NEAR/2 (technique* OR surger* OR operat* OR procedure* OR reimplan* OR repair* OR intervention* OR tirone* OR resuspens*)) OR david-type OR david-i OR david-1 OR david-ii OR david-2 OR david-v OR david-5))) NOT DT=(Meeting Abstract OR Meeting Summary) AND LA=(english)

Google Scholar

Aorta|aortic|Valsalva|root "valve sparing|spare|preserving|reimplantation"|"david technique|surgery |operation|procedur e|reimplantation|repair|intervention|resuspension|type"

Appendix 2

Background mortality

For the overall group and bicuspid/tricuspid subgroup separately, the background mortality of the general population was acquired for the pooled median year of intervention within each country among included studies from that country. Country, year and sex-specific background mortality estimates were obtained from the Human Mortality Database (https://www.mortality.org/). Brazil, Turkey and China are not included in this database, but only 8% of included patients originated from these countries, and they were not present in the subgroups. Proportion of individuals of the included countries are presented in Table S3. Survival was matched with the corresponding year and sex-specific background survival in the countries of origin separately for each subgroup.

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Excess mortality

We compared the survival simulated by the microsimulation model with the observed survival in our Kaplan-Meier meta-analysis for time-to-event outcomes to estimate the risk ratio of additional excess mortality not directly resulting from valve-related morbidity relative to the probability of background mortality observed in the general population. We temporarily excluded early mortality, since early mortality was a separate input in our microsimulation model. During the simulation, we iteratively simulated the survival of 10.000 patients with an age deriving from the mean ± SD distribution and proportion of males of the study population using the same mortality due to valve-related events and background mortality, but with varying risk ratios of excess mortality for different timeframes. Subsequently, the risk ratio resulting in the smallest difference between the simulated and observed survival according to the least squares method was chosen as the suitable risk ratio for excess mortality. The iterative procedure (by minimizing least squares) is based on the golden section search method (Kiefer, J. (1953), "Sequential minimax search for a maximum").

Probabilistic sensitivity analysis (PSA)

Probabilistic sensitivity analysis (PSA) was performed to consider the uncertainty in input parameters of our microsimulation and to reflect the implications for uncertainty in outcomes. In the PSA, the model considered a sample size of 1,000 patients per set and ran for 1000 different sets of randomly drawn input parameters. Values of the input parameters were randomly drawn from the following distributions: beta distributions for early mortality risk and probabilities of re-interventions and death after valve-related events, log-normal distributions for late events and normal distributions for the RR of mortality after reintervention and excess mortality, varied with +/-10%. For all sets of coefficients, the mean outcome in the 1000 patients was recorded and the mean (point estimate) and the 2.5% and 97.5% percentiles (credible interval) over all the 1000 mean values for each outcome were computed. PSA allows the microsimulation to take into account both first-order uncertainty (random variation in outcomes between identical patients) and second-order uncertainty (uncertainty in the input parameters).

Appendix 3

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Table S1 Input parameters microsimulation and their source

Parameter	Source
Baseline	
Age	Sample size weighted summarized age
SD Age	Sample size weighted summarized SD age
Sex	Proportion of males included studies
Early events	
Early mortality	Meta-analysis (pooled proportion)
Early endocarditis	Meta-analysis (pooled proportion)
Early Valve thrombosis	Meta-analysis (pooled proportion)
Early bleeding	Meta-analysis (pooled proportion)
Early MI	Meta-analysis (pooled proportion)
Risk ratio early mortality reintervention	Calculated by dividing early mortality by mortality due to AV reintervention
Late events	
Late mortality (background)	HMD life tables
Observed mortality	Reconstructed-IPD KM of late mortality
Late mortality excess mortality risk ratio	Calculated by difference between background mortality + valve related mortality and observed mortality
Late mortality valve related	Mortality caused by early mortality, late bleeding, late stroke, late endocarditis, overall AV reintervention
Late AV reintervention	Reconstructed-IPD KM of overall AV reintervention*
Late Bleeding	Meta-analysis (pooled adverse event rate)
Late Stroke	Meta-analysis (pooled adverse event rate)
Late endocarditis	Meta-analysis (pooled adverse event rate)
Late Valve thrombosis	Meta-analysis (pooled adverse event rate)
Consequences of events	
Reintervention due to endocarditis	Summarized proportion reported intervention for endocarditis
Reintervention due to valve thrombosis	Summarized proportion reported intervention for endocarditis
Mortality due to bleeding	Summarized proportion reported mortality for bleeding
Mortality due to stroke	Summarized proportion reported mortality for stroke
Mortality due to endocarditis	Summarized proportion reported mortality for endocarditis
Mortality due to valve thrombosis	Summarized proportion reported mortality for valve thrombosis
Mortality due to AV reintervention (only used to calculate RR early mortality intervention)	Summarized proportion reported mortality for AV reintervention

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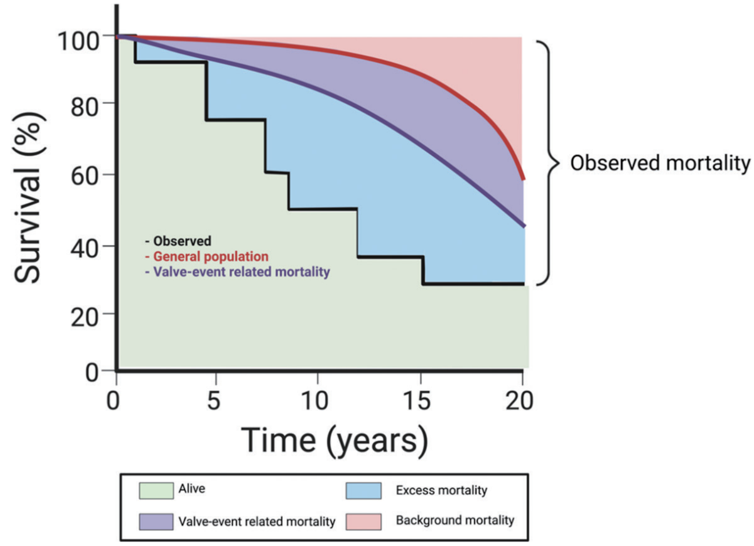

Figure S1 Explanation of different microsimulation based sources of mortality. Background mortality is mortality in the matched background population. Valve-related event mortality is the mortality due to valve related events (AV reintervention, endocarditis, stroke, thrombo-embolism, bleeding, valve-thrombosis). Excess mortality is the additional mortality patients exhibit minus valve related event mortality and background mortality.

Table S2 Estimated risk ratios of excess mortality for specific timeframes

Group	0–3 months	4–12 months	13–120 months	121–240 months
Total group	3.754	3.754	0.88	0.981
BAV group	0.43	0.43	0.43	0.43
TAV group	11.5	0.96	0.96	0.96

BAV, Bicuspid aortic valve; TAV, tricuspid aortic valve.

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Table S3 Proportion of individuals from included countries

Country	Year	Overall group		Bicuspid subgroup		Tricuspid subgroup	
		Proportion	Adjusted proportion	Proportion	Adjusted proportion	Proportion	Adjusted proportion
Belgium	2008	4.2%	4.4%	12.5%	12.5%	14.3%	14.3%
Brazil	–	2.1%	0.0%	0.0%	0.0%	0.0%	0.0%
China	–	4.2%	0.0%	0.0%	0.0%	0.0%	0.0%
Canada	2004	2.1%	4.4%	0.0%	0.0%	0.0%	0.0%
Finland	2011	2.1%	2.2%	12.5%	12.5%	0.0%	0.0%
France	2011	6.3%	6.7%	12.5%	12.5%	0.0%	0.0%
Germany	2011	25.0%	26.7%	0.0%	0.0%	14.3%	14.3%
Italy	2007	12.5%	13.3%	0.0%	0.0%	14.3%	14.3%
Japan	2018	4.2%	4.4%	0.0%	0.0%	0.0%	0.0%
Lithuania	2010	2.1%	2.2%	0.0%	0.0%	0.0%	0.0%
Netherlands	2008	2.1%	2.2%	0.0%	0.0%	0.0%	0.0%
Poland	2015	2.1%	2.2%	0.0%	0.0%	0.0%	0.0%
Korea	2004	2.1%	2.2%	0.0%	0.0%	14.3%	14.3%
Spain	2011	4.2%	4.4%	0.0%	0.0%	0.0%	0.0%
Switzerland	2015	2.1%	2.2%	0.0%	0.0%	14.3%	14.3%
Turkey	–	2.1%	0.0%	0.0%	0.0%	0.0%	0.0%
USA	2009	20.8%	22.2%	62.5%	62.5%	28.6%	28.6%

Table S4 Types of distribution fit to pooled time-to-event data for all time-varying risks in the microsimulation model

Bicuspid aortic valve	Linearized occurrence rate
Tricuspid aortic valve	Gamma distribution
Total group	Royston-Parmar distribution

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Table S5 Pre and perioperative characteristics in TAV and BAV

Variable	Pooled Data	Range	Included Studies (n)	Included Patients (n)
Tricuspid Aortic Valve (TAV)				
Total patient number (n)	2054	58–448	11	2054
Surgical period (years)	1995–2020		11	2054
Age (years), mean ± SD	48.6±14.2	36–57.5	10	1996
Gender, male (%)	80.7	56.9–93.1	11	2054
Comorbidity				
Renal insufficiency (dialysis) (%)	0.6	0–0.9	3	482
LV dysfunction (EF <30%)	2.9	1.3–6.4	3	375
Hypertension (%)	50.1	22.0–79.4	8	1365
Coronary artery disease (%)	16.3	2.9–38.1	6	1106
Connective tissue disease (%)	30.2	0–100	8	1112
Bicuspid aortic valve (%)	0	0	11	2054
Prior cardiac operation (%)	4.9	0–16.2	6	1424
Emergency surgery (%)	3.3	0–17.2	9	1965
Reexploration for bleeding (%)	5.0	0–15.9	10	1884
Concomitant procedure (n)	745	14–168	10	1726
Mitral valve plasty (%)	7.0	1.4–9.8	10	1726
Mitral valve replacement (%)	0.2	0–1.7	7	982
Tricuspid valve surgery (%)	1.7	0–6.4	7	1262
CABG (%)	9.5	0–23.6	10	1726
Hemiarch repair (%)	20.7	9.5–90.2	6	916
Arch repair (%)	12.0	1.9–10.0	7	903
Other (VSD repair, MAZE etc.) (%)	8.9	1.9–25.3	9	1637
Extracorporeal circulation time, min., mean ± SD	164.3±40.6	127–227	11	2054
Aortic cross-clamping time min., mean ± SD	133.9±30.6	99–231	11	2054
Bicuspid Aortic Valve (BAV)				
Total patient number (n)	865	29–189	12	865
Surgical period (years)	1993–2022		12	865
Age (years), mean ± SD	44.0±12.3	40.1–47.4	12	865
Gender, male (%)	89.1	79.4–100	12	865
Comorbidity				
Renal insufficiency (dialysis) (%)	0	0	3	190
LV dysfunction (EF <30%)	0	0	2	246
Hypertension (%)	41	17.5–79.5	12	865
Coronary artery disease (%)	8.7	3.5–20.7	4	254
Connective tissue disease (%)	3.8	0–9.1	6	426
Bicuspid aortic valve (%)	100	100	12	865
Prior cardiac operation (%)	2.6	0–6.4	8	628
Emergency surgery (%)	1.6	0–4.6	8	506
Reexploration for bleeding (%)	2.5	0–5.1	9	556
Concomitant procedure (n)	321	0–63	12	865
Mitral valve plasty (%)	2.2	0–7.2	11	808
Mitral valve replacement (%)	0	0	8	562
Tricuspid valve surgery (%)	0.2	0–0.5	8	645
CABG (%)	5.00	0–10.3	11	808
Hemiarch repair (%)	20.1	0–64.1	7	603
Arch repair (%)	22.6	0–76.2	9	541
Other (VSD repair, MAZE etc.) (%)	2.8	0–11.1	9	690
Extracorporeal circulation time, min., mean ± SD	190.9±33.8	122–309	12	865
Aortic cross-clamping time min., mean ± SD	159.8±27.1	97–242	12	865

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Table S6 Univariable meta regression for re-exploration for bleeding and late mortality

Characteristic	B estimate (SE)	P-value	% heterogeneity explained
Re-exploration for bleeding			
Mean year of surgery	0.05 (0.03)	0.10	0%
Age	0.04 (0.01)	0.002	26%
Males (per 1% increase)	0.01 (0.01)	0.32	0%
Mean follow-up years	0.02 (0.05)	0.64	0%
BAV (vs TAV) (per 1 % increase)	–0.01 (0.01)	0.16	1%
Cardiopulmonary bypass time	–0.004 (0.003)	0.08	0%
Late mortality			
Mean year of surgery	–0.03 (0.03)	0.35	0%
Age	0.06 (0.01)	<.001	50%
Males (per 1% increase)	0.03 (0.02)	0.03	0%
Mean follow-up years	0.02 (0.06)	0.70	0%
BAV (vs TAV) (per 1 % increase)	–0.003 (0.004)	0.39	9%
Cardiopulmonary bypass time	–0.004 (0.002)	0.03	1%

BAV, Bicuspid aortic valve; TAV, tricuspid aortic valve.

Table S7 Pooled early risks and linearized occurrence rates of the total group after temporarily excluding studies with the lowest 25th sample size or patient years (in case of late outcomes)

Outcome	Risk (%)	95% CI	Studies included (n)
Early Outcomes			
Early mortality	1.5	1.1–1.9	33
Reintervention on the aortic valve	0.4	0.3–0.6	24
Reexploration for bleeding	5.1	4.1–6.4	30
Stroke	0.9	0.6–1.4	27
Late Outcomes			
Late mortality	0.86	0.67–1.11	28
Reintervention on the aortic valve	0.67	0.52–0.86	25
Endocarditis	0.21	0.14–0.30	26
Stroke	0.22	0.16–0.33	20
Bleeding	0.14	0.07-0.29	14

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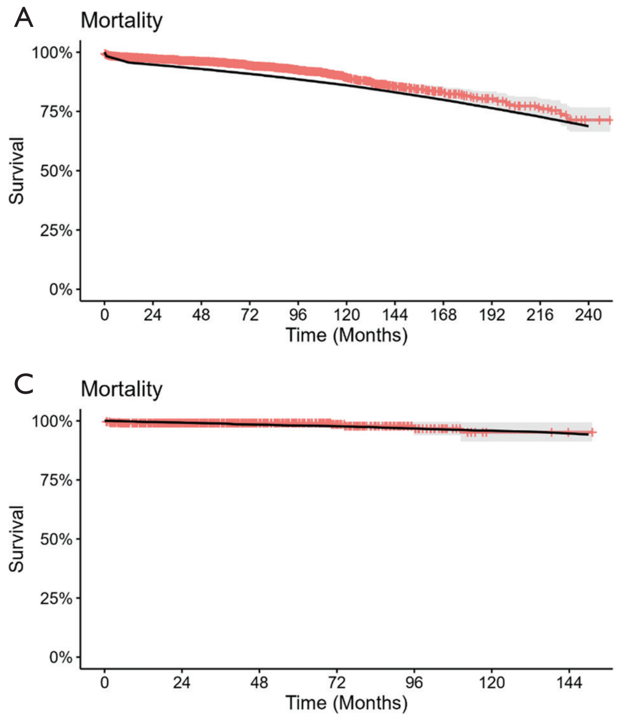

Figure S2 Calibration plots of microsimulation based mortality (black line) and observed mortality (KM curves, red line) for total group (A), bicuspid group (B) and tricuspid group (C).

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