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META-ANALYSIS
Congenital heart disease

Paediatric aortic valve replacement: a meta-analysis and microsimulation study

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Abstract

Aims To support decision-making in children undergoing aortic valve replacement (AVR), by providing a comprehensive overview of published outcomes after paediatric AVR, and microsimulation-based age-specific estimates of outcome with different valve substitutes.

Methods and results A systematic review of published literature reporting clinical outcome after paediatric AVR (mean age <18 years) published between 1/1/1990 and 11/08/2021 was conducted. Publications reporting outcome after paediatric Ross procedure, mechanical AVR (mAVR), homograft AVR (hAVR), and/or bioprosthetic AVR were considered for inclusion. Early risks (<30d), late event rates (>30d) and time-to-event data were pooled and entered into a microsimulation model. Sixty-eight studies, of which one prospective and 67 retrospective cohort studies, were included, encompassing a total of 5259 patients (37 435 patient-years; median follow-up: 5.9 years; range 1–21 years). Pooled mean age for the Ross procedure, mAVR, and hAVR was 9.2 ± 5.6, 13.0 ± 3.4, and 8.4 ± 5.4 years, respectively. Pooled early mortality for the Ross procedure, mAVR, and hAVR was 3.7% (95% CI, 3.0%–4.7%), 7.0% (5.1%–9.6%), and 10.6% (6.6%–17.0%), respectively, and late mortality rate was 0.5%/year (0.4%–0.7%/year), 1.0%/year (0.6%–1.5%/year), and 1.4%/year (0.8%–2.5%/year), respectively. Microsimulation-based mean life-expectancy in the first 20 years was 18.9 years (18.6–19.1 years) after Ross (relative life-expectancy: 94.8%) and 17.0 years (16.5–17.6 years) after mAVR (relative life-expectancy: 86.3%). Microsimulation-based 20-year risk of aortic valve reintervention was 42.0% (95% CI: 39.6%–44.6%) after Ross and 17.8% (95% CI: 17.0%–19.4%) after mAVR.

Conclusion Results of paediatric AVR are currently suboptimal with substantial mortality especially in the very young with considerable reintervention hazards for all valve substitutes, but the Ross procedure provides a survival benefit over mAVR. Pros and cons of substitutes should be carefully weighed during paediatric valve selection.

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Structured Graphical Abstract

Key Question

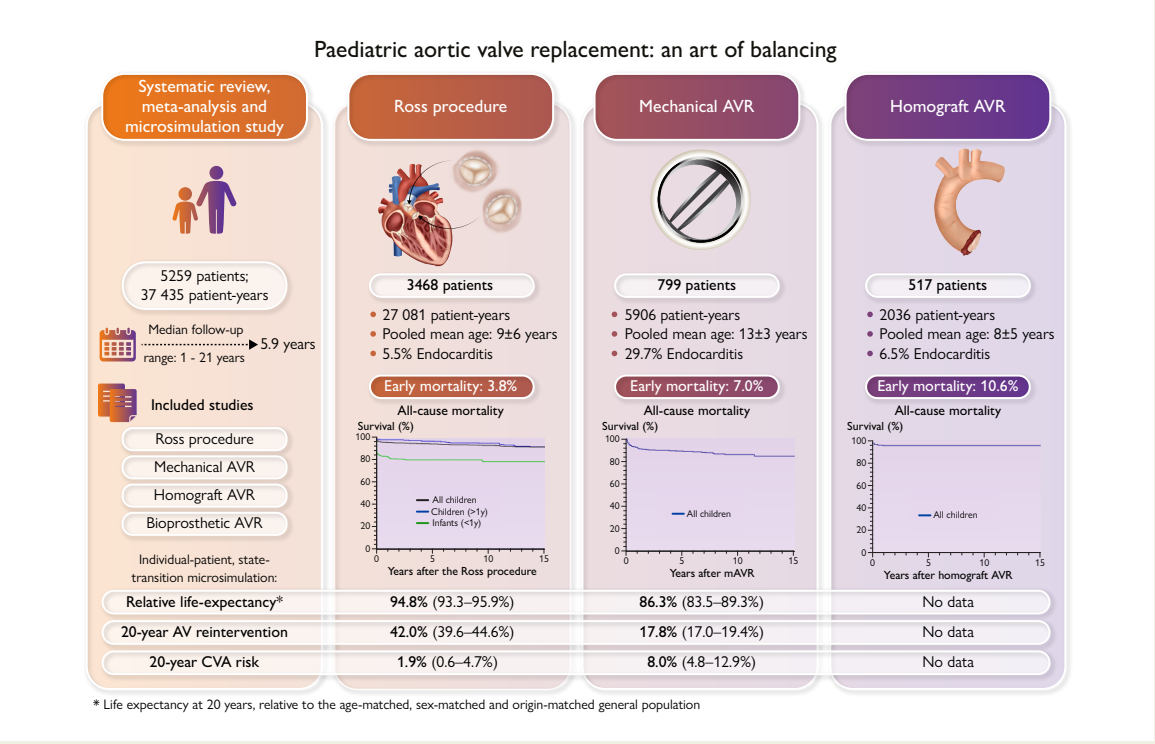
What characterizes contemporary outcome after the Ross procedure, mechanical aortic valve replacement (AVR), homograft AVR and bioprosthetic AVR in paediatric patients?

Key Finding

The Ross procedure offered survival closest to the general population and a low incidence of valve-related events such as bleeding when compared to mechanical AVR in children. Nonetheless, reintervention hazards were highest after Ross. Microsimulation-based estimates provided opportunities to communicate essential information to patients.

Take Home Message

Valve selection requires careful balancing of all benefits and risks. Current outcomes of AVR in children are suboptimal and an ideal substitute for the aortic valve does not exist. Nonetheless, the Ross procedure offers a survival benefit over mechanical AVR.
These data confirm the benefits of a living aortic valve substitute in children.



Summary of clinical outcome after paediatric aortic valve replacement (AVR) with a pulmonary autograft (Ross procedure), mechanical prosthesis, or homograft.

Keywords Aortic valve • Congenital heart disease • Aortic valve replacement • Microsimulation

Introduction

Aortic valve (AV) disease in children calls for lifelong monitoring and management. Although valve repair should always be considered in children requiring AV surgery, the majority of paediatric patients inevitably require AV replacement (AVR).[1–3] Using repair techniques, a haemodynamically acceptable and durable result is only achieved in a small proportion of patients.[4] Outcome of valve-replacing therapies in children is largely dependent on somatic growth, in addition to valve-related morbidity. Four different valve substitutes are currently available.

The pulmonary autograft procedure was introduced by Donald Ross in 1967[5] and became an established treatment modality for AV disease (AVD), known as the Ross procedure. This rapidly became the substitute of choice in children[1,6,7] since it is the only living valve substitute that mimics native AV function,[8,9] shows diameter increase along with somatic growth, alleviates the need for lifelong anticoagulation, and yields excellent haemodynamics.[10–12] In adults, it provides patients with a life expectancy comparable to the general population.[8,13,14] However, the Ross procedure is technically demanding, transforms single-valve disease to double-valve disease and the autograft is at risk for dilatation. Secondly, implantation of a mechanical prosthesis for

AVR (mAVR) may be considered.[15] Durability of mechanical prostheses is excellent[16] and they are widely commercially available, but they require lifelong anticoagulation and do not adapt to somatic growth. Additionally, homograft AVR (hAVR) was proposed as a treatment for AVD by Ross in the early 1960s.[17] Homografts bring the advantage of a nonthrombogenic substitute while offering patients a native human valve, but they exhibit limited availability and durability due to early structural degeneration. Finally, bioprostheses are commercially available as a substitute, but limited durability and absent growth potential represent drawbacks in children.

Since the publication of a prior systematic review on outcome after AVR in children by our group in 2016,[1] an abundance of new publications reporting on paediatric cohorts undergoing AVR with longer follow-up have been published. Furthermore, our group has implemented advanced methods of microsimulation[11,18–20] and meta-analysis of time-to-event data[21] that allow for a substantially more accurate insight into long-term, patient-specific outcome.

Therefore, to support decision-making in AVD in children, the aim of this systematic review and meta-analysis is to provide an overview of currently available evidence on early and late survival, reintervention, and valve-related outcomes after paediatric Ross procedure, mAVR, hAVR, or bioprosthetic AVR (bAVR).

Methods

Protocol and registration

The protocol for this systematic review and meta-analysis was approved by the local medical ethics committee of the Erasmus University Medical Center (MEC-2021–0784), registered in the PROSPERO registry (CRD42021271660) prior to conduction and reported in accordance with the updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[22] (see *Supplement S1*) and Meta-Analysis of Observational Studies in Epidemiology guidelines.[23]

Search strategy and selection of studies

MEDLINE, Embase, Web of Science, Cochrane Library, and Google Scholar were searched by a biomedical information specialist using keywords related to AVR in infants, children and/or adolescents published between 1 January 1990 and 11 August 2021. The search string is listed in *Supplement S1*. Titles and abstracts were independently screened by two reviewers (M.L.N., A.S.) and in case of disagreement, an agreement was reached through consensus. Full-text screening was performed independently by two reviewers (M.L.N., A.S.), adhering to identical exclusion criteria. Inclusion criteria were observational or randomized controlled studies reporting outcomes after isolated AVR with a pulmonary autograft (Ross), homograft, mechanical- or biological prosthesis concerning ≥20 patients with a mean age <18 years and maximum age ≤21 years during AVR. Studies focusing on patients with a certain annulus/root size, history of previous AVR and studies limited to patients with comorbidities were excluded. Single-arm studies were considered for inclusion. If the full text was not available, the publication was obtained by either contacting the corresponding author or by an interlibrary loan procedure established among universities.

Presence of methodological heterogeneity/diversity, potentially leading to statistical heterogeneity, was evaluated by investigating similarity of studies according to the PICOTS framework.

Risk of bias assessment

Quality and risk of bias of individual studies was assessed according to the Newcastle-Ottawa scale for cohort studies. Completeness of follow-up ≥80% was considered adequate and mean follow-up ≥5 years was considered sufficient for outcomes to occur. Domains evaluated by the risk of bias assessment tool were patient selection and outcome reporting. The comparability domain was not evaluated as all cohorts were treated as single arms in the meta-analysis.

Data extraction

Data extraction was performed independently by two reviewers (M.L.N., A.S.) using Microsoft Office Excel 2016 (Microsoft Corp., Redmond, WA, USA). All extracted data were verified by another reviewer. In case of disagreement on any of the reported values, an agreement was reached through consensus. All extracted study, patient and surgical characteristics and outcomes are enclosed in *Supplement S1*.

Meta-analysis outcomes

Pre- and postoperative functional class were defined according to the Ross classification of heart failure for children[24] or the New York Heart Association (NYHA) classification, as described by the authors. Early and late outcomes were documented according to the guidelines by Akins and colleagues[25] and are listed in *Supplement S1*. Early outcome events were defined as events occurring within the first 30 days after AVR and late outcome events as events occurring after the first 30 days after AVR.

Statistical analyses

The statistical software used is described in *Supplement S1*. Continuous variables are presented as mean ± standard deviation (SD). Categorical variables are presented as counts and percentages. Linearized occurrence rates (constant hazards over time) of events are presented as percentages per year. All single-arm publications and cohorts within multi-arm publications were categorized by valve type: autograft (Ross), hAVR, mAVR, and bAVR. Cohorts consisting of only infants (<1 year) and neonates (<30 days) were pooled separately. Baseline and surgical characteristics were summarized as a weighted average based on sample size. Inverse variance weighting was carried out for pooling event proportions (early events), according to the number of patients, and occurrence rates (late events), according to the number of patient-years. Early and late outcomes (proportions and occurrence rates) were pooled on a logarithmic scale. Between-study variance was estimated according to the DerSimonian and Laird method in a random-effects model.[26] In case an event did not occur, we assumed that 0.5 patients in this cohort experienced the event for pooling purposes (continuity correction). Subgroup analyses were performed for (sub)cohorts consisting of infants (<1 year) and those consisting of consecutive children (<18 years), as well as for additional Konno (aorto-ventriculoplasty) procedures[27] and procedures without any left ventricular outflow tract (LVOT) enlargement. $P < 0.05$ were considered statistically significant.

Estimates of time-to-event data, derived from published Kaplan–Meier curves, were extracted and combined using the method described by Guyot.[28] Firstly, published Kaplan–Meier curves for survival, LVOT reintervention, and right ventricular outflow tract (RVOT) reintervention were digitized. Subsequently, the estimated time-to-event data were extracted from this digitized curve. Lastly, the reconstructed time-to-event data of studies were combined for each time-to-event outcome, to generate pooled Kaplan–Meier curves. A detailed overview of the methodology is presented in *Supplement S1*.

A sensitivity analysis for survival and reintervention was performed (see *Supplement S1*) by comparing estimates derived from Kaplan–Meier pooling excluding any text-derived time-to-event data reconstruction vs. estimates derived from Kaplan–Meier pooling with additional text-derived time-to-event data reconstruction (i.e. zero events reported).

The Cochran Q-statistic and I^2-statistic were used to assess the proportion of total heterogeneity in an outcome attributable to between-study heterogeneity. Univariable random effects meta-regression was performed to evaluate causes of heterogeneity within outcome measures. The effect of patient characteristics, surgical details (see *Supplement S1*)

and median year of surgery on outcomes was investigated by meta-regression. Presence of publication bias was explored by conducting sensitivity analysis, in which the quartile of studies with the smallest sample size was temporarily excluded. These results were compared to the pooled results including all studies.

Microsimulation

Microsimulation models provide insight into age-specific life expectancy and lifetime risk of valve-related events that may occur during the particular remaining life of that particular patient.[29] An individual-patient state-transition microsimulation model based on the pooled early and late outcome estimates of our meta-analysis was employed to estimate age-specific life expectancy and age-specific risks of valve-related morbidity after paediatric AVR (see *Supplement S1*). Since follow-up duration was too short to make inferences about lifetime risks after paediatric AVR, the occurrence of all valve-related events was simulated to the extent of the observation period this meta-analysis (20 years). All outcomes of the meta-analysis that subsequently served as input for the microsimulation, model structure, equations, and all functions used in the simulation (technical documentation) are explained in *Supplement S1* and the Supplementary Microsimulation. Recommendations for reporting simulation studies were checked to ensure good practice, transparency, and validation of the model.[30,31]

The occurrence of all-cause and structural valve deterioration (SVD)-related AV reintervention was modelled according to the flexible parametric survival model that fitted the time-to-event data of each outcome best (see *Supplement S2*). No time-to-event data were available for other valve-related events (endocarditis, cerebrovascular accident, bleeding, valve thrombosis, thromboembolism); therefore, we assumed constant hazards for these events.

All-cause mortality was simulated and can be divided into death directly due to valve-related events vs. death not directly due to valve-related causes. The latter consists of both background mortality in the general population and excess mortality that does not directly result from valve-related events but is only observed after AVR. Methods for estimating background mortality and additional details of the estimation of excess mortality are described in *Supplement S1*.

In order to obtain age-specific estimates of life expectancy and 20-year risks of valve-related complications after the Ross procedure, the microsimulation simulated cohorts of 10 000 patients aged <1 year or <18 years, of which 71.2% and 70.7% were male, respectively (pooled male proportions).

Probabilistic sensitivity analysis was performed to take the uncertainty in input parameters of our microsimulation into account and incorporate the implications of this uncertainty into the modelled outcomes. In the sensitivity analysis, the model considered a sample size of 1000 patients per set and ran for 500 different sets of randomly drawn input parameters. Microsimulation-based outcomes are reported along with a 95% credible interval (CrI), the interpretation of which differs from a 95% confidence interval (CI). The 95% CrI represents the range of values (interval) within which an unobserved parameter will fall with 95% probability given the observed data, thus the bounds being fixed and parameters random. The 95% CI entails that in a large numbers of repeated samples, 95% of the intervals include the true value, the parameter being fixed and bounds random. Additional insights into the probabilistic sensitivity analysis are provided in *Supplement S1*.

For the purpose of internal validity assessment of late survival and reintervention outcomes of this model, the model was run for 10 000 patients with the distribution of the pooled mean ± SD of age and proportion of males for all subgroups of studies included in the pooled Kaplan–Meier for late mortality. The Kaplan–Meier survival curve obtained from this microsimulation (excluding early mortality) was plotted against the pooled Kaplan–Meier survival curve derived from our meta-analysis in a calibration plot (excluding early mortality) to confirm calibration.

Results

Systematic review

A total of 3807 publications were identified by the systematic literature search, of which 68 (67 retrospective cohort studies and 1 prospective cohort study) were included in the meta-analysis (*Figure 1*), encompassing a total of 5259 patients with 37 435 patient-years of follow-up. Median follow-up was 5.9 years (range:1–21 years). Only one study on bAVR was identified.[32] References of included studies and individual study characteristics are listed in *Supplement S3* and *S4*, respectively.

Quality and risk of bias assessment for cohort studies revealed that 32% of studies scored 7/7 points (100% of points). Another 49% of studies scored 6/7 points (86% of points), 15% scored 5/7 points (71% of points) and 4% scored 4/7 points (57% of points). Total and substitute-specific quality assessment is enclosed in *Supplement S1.3*.

Meta-analysis

Baseline characteristics and operative details for each substitute are summarized in *Table 1*. Baseline characteristics for the Ross–Konno and infant Ross cohorts are summarized in *Supplement S5*.

Pooled early mortality after Ross, mAVR, and hAVR was 3.7% (95% CI: 3.0%–4.7%), 7.0% (95% CI: 5.1%–9.6%), and 10.6% (95% CI: 6.6%–17.0%), respectively. Pooled late mortality rates after Ross, mAVR, and hAVR, were 0.5%/year (95% CI: 0.4%–0.7%/year), 1.0%/year (95% CI: 0.6%–1.5%/year), and 1/4%/year (95% CI: 0.8%–2.5%/year), respectively. Pooled early outcome risks and pooled occurrence rates of late mortality and valve-related events are listed in *Table 2*. Pooled outcomes for the Ross–Konno and infant Ross cohorts (see *Supplement S6*) as well as all individual study estimates (see *Supplement S7* and *S8*) are enclosed in the Supplement.

Similarity of included studies was evaluated for each study by the PICOTS statement (see *Supplement S14*). Substantial statistical heterogeneity was observed for several late outcomes after the Ross procedure and mAVR, mainly for late mortality, AV reintervention, and allograft reintervention (*Table 2*). Individual estimates of the univariable random-effects meta-regression for each outcome after the Ross procedure and mAVR are listed and summarized in *Supplement S12*.

Fifteen-year freedom from LVOT reintervention after Ross and mAVR was 77.6% and 88.7%, respectively. Pooled Kaplan–Meier curves of freedom from all-cause mortality, LVOT reintervention and RVOT reintervention are presented in *Figure 2*.

Within all twelve studies reporting NYHA functional class at last follow-up after the Ross procedure (median follow-up: 5.8 years, range: 2.8–20.5 years), 95.2% of the patients were in NYHA class I/II.

Sensitivity analysis

Sensitivity analyses revealed that possible publication bias did not considerably influence the pooled outcome estimates of our meta-analysis for the Ross procedure, mAVR, and hAVR, since pooled outcome estimates remained largely unchanged after excluding the smallest quartile of studies by sample size. The results of sensitivity analyses are presented in *Supplement S11*.

Sensitivity analyses of Kaplan–Meier reconstruction with or without additional text-derived time-to-event data are presented in *Supplement S13*. Removal of text-derived time-to-event data revealed a change in 15-year freedom from reintervention from 81.0% to 59.4%. As the pooled occurrence rate of LVOT reintervention was lower in infants (1.0%/year) than in children (1.3%/year), the Kaplan–Meier that includes text-derived time-to-event data more accurately approximates reintervention rates.

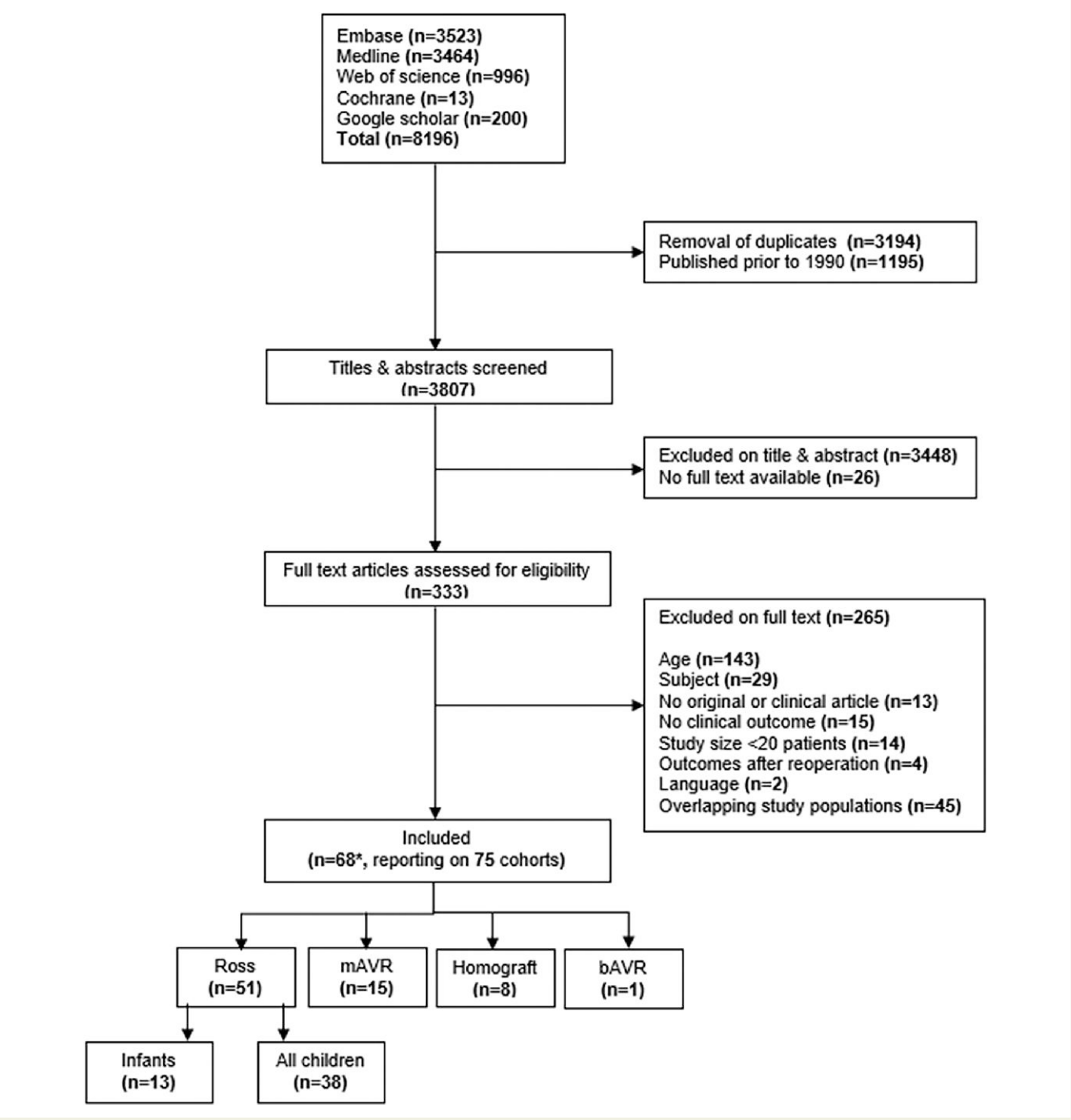


Figure 1 Flowchart of study selection. * The total number of publications ($n = 68$) includes three publications from which only Kaplan–Meier curves were used. Baseline characteristics and outcome estimates of these publications are not provided due to overlapping study populations with other publications included in this meta-analysis.

Microsimulation outcomes

Microsimulation-based age-specific estimates of (event-free) life expectancy and age-specific 20-year risks of valve-related morbidity are presented in *Table 3* and *Figures 3* and *4*. The microsimulation model calibration with the pooled mortality and reinterventions resulting from the meta-analysis are available in *Supplement S9*. Analysis of survival estimates from the microsimulation model (excluding early mortality) vs. the estimates obtained from our meta-analysis of time-to-event data (excluding early mortality) revealed a HR for excess mortality of 2.2, 1.8, and 1.2 for mAVR, the Ross procedure and the infant Ross procedure, respectively (see *Supplement S10*).

For children undergoing mAVR, mean life expectancy in the first 20 postoperative years was 86.3% (95% CrI: 83.5%–89.3%) relative to the age- and sex-matched general population. For children undergoing a Ross procedure, mean life expectancy in the first 20 postoperative years was 94.8% (CrI: 93.3%–95.9%) relative to the matched general

Table 1 Summary of baseline characteristics and surgical details

	Ross		Mechanical		Homograft	
	Pooled estimate	Number of studies	Pooled estimate	Number of studies	Pooled estimate	Number of studies
Total number of patients	3468	38	799	15	517	8
Follow-up						
Mean, y	8.1 ± 6.0	37	7.3 ± 4.6	15	5.4 ± 5.4	6
Total, patient-years	27080.7	37	5906	15	2036.1	6
Mean age (years)	9.2 ± 5.6	33	13.0 ± 3.4	11	8.4 ± 5.4	6
Male	70.7% (60.5–91.7)	27	75.3% (58.3–84.5)	7	67.7% (63.5–72.6)	3
Urgent	6.6% (2.4–14.8)	7	–	0	–	0
Preop. NYHA/Ross class						
I	52.2% (48.6–56.3)	2	–	0	–	0
II	35.8% (34.4–37.1)	2	–	0	–	0
III	10.5% (9.4–11.4)	2	–	0	–	0
IV	1.5% (0.0–2.9)	2	–	0	–	0
I/II	83.5% (78.3–91.6)	3	–	0	–	0
III/IV	16.5% (9.4–21.7)	3	–	0	–	0
Hemodynamics						
Aortic stenosis	34.9% (11.6–89.1)	30	30.7% (6.1–60.3)	7	39.6% (21.7–66.0)	3
Aortic regurgitation	24.6% (8.8–59.2)	30	54.2% (20.7–87.8)	7	30.4% (10.6–43.3)	3
Combined	42.0% (9.3–75.8)	27	15.1% (6.1–21.8)	7	30.0% (14.4–51.8)	3
Bicuspid AV	56.4% (33.4–78.2)	20	54.0% (50.9–56.9)	2	–	0
Etiology						
Congenital	79.6% (66.6–100.0)	24	60.3% (11.5–98.2)	9	–	0
Endocarditis	5.5% (0.0–30.9)	23	29.7% (0.0–74.1)	9	6.5% (0.0–18.1)	3
Rheumatic	2.7% (0.0–10.9)	24	6.1% (0.0–19.0)	9	–	0
Other/unknown	12.3% (0.0–100.0)	27	3.9% (0.0–9.2)	9	–	0
Concomitant anomalies	27.9% (12.2–36.7)	8	28.2% (10.9–50.0)	4	43.3% (32.5–55.4)	2
Aortic coarctation	9.0% (2.9–16.8)	9	2.4% (0.0–5.5)	3	–	1
Ventricular septal defect	6.3% (0.9–15.9)	10	8.9% (1.8–13.8)	4	–	1
Interrupted aortic arch	4.5% (2.0–6.1)	4	0.9% (0.0–1.8)	2	–	1
Previous cardiac interventions	53.4% (34.9–80.4)	12	43.1% (7.3–64.3)	7	58.0% (43.7–89.4)	2
AV intervention	53.8% (18.3–81.3)	19	27.1% (5.5–52.3)	4	42.9% (37.4–51.9)	4
Percutaneous	27.2% (9.1–58.7)	20	3.3% (0.0–16.7)	4	33.3% (27.0–37.7)	2
AV repair	29.1% (0.0–56.5)	18	26.0% (5.5–40.0)	4	–	1
AV replacement	1.8% (0.0–8.7)	15	1.5% (0.0–5.6)	4	13.7% (6.4–17.0)	2
SAS resection	9.4% (0.0–24.5)	11	3.7% (0.0–7.3)	3	–	1
Aortic surgery	12.7% (2.9–29.4)	9	4.1% (1.8–8.3)	3	–	1
Coarctectomy	6.3% (0.0–12.0)	6	2.8% (1.8–3.7)	2	–	0
VSD closure	5.5% (0.0–9.8)	10	1.8% (0.0–3.7)	3	–	1

Continued

Table 1 *Continued*

	Ross		Mechanical		Homograft	
	Pooled estimate	Number of studies	Pooled estimate	Number of studies	Pooled estimate	Number of studies
Annular enlargement procedures	16.5% (0.0–36.7)	28	27.4% (2.3–100.0)	11	24.0% (8.4–70.2)	3
SAS resection during AVR	6.4% (0.0–18.9)	17	5.0% (0.0–12.0)	7	34.7% (0.0–70.2)	2
Concomitant procedures	24.8% (0.0–44.4)	13	39.1% (10.0–82.4)	9	–	1
Aortic surgery	10.3% (0.0–29.8)	15	8.8% (0.0–21.6)	7	–	1
Other valve surgery	4.3% (0.0–19.4)	15	11.9% (5.4–24.1)	7	13.9% (3.8–24.3)	2
Other concomitant surgery	12.4% (0.0–30.0)	14	4.6% (0.0–22.2)	7	–	1

population. For infants undergoing a Ross procedure, mean life expectancy in the first 20 postoperative years was 84.0% (CrI: 81.1%–86.9%) relative to the matched general population.

Discussion

Valve selection in young patients who potentially have a long life ahead remains a complex topic. Focus should lie on determining what substitute will ensure optimal outcome in the individual child in need of AV surgery not amenable to repair, from both a clinical and patient perspective. The current study adds to the ever-growing body of evidence on the management of valvular heart disease that current options for paediatric AVR are far from perfect. Through the microsimulation, it shows that valve selection in children remains a delicate balancing act between substitute-specific risks and benefits.

The Ross procedure provides children with excellent haemodynamics and low rates of endocarditis, valve thrombosis, thrombo-embolism, and bleeding compared to prosthetic valves but transforms single-valve disease to double-valve disease at a young age[33] and comes at the cost of a moderate LVOT reintervention rate and high RVOT reintervention rate due to conduit deterioration. Contrarily, mAVR puts patients at substantial risk for valve-related complications such as bleeding and valve-thrombosis given thrombogenicity of the prosthesis and subsequent need for anticoagulation. The hazard of reintervention for SVD is low after mAVR given excellent durability.[16] Although patient selection may play a role, hAVR was associated with the highest mortality and reintervention rates. The single study reporting outcome after bAVR included 24 children deemed no Ross candidates.[32] They reported no deaths and one reoperation (0.3%/year), although follow-up was short (mean follow-up: 46 months). These are good outcomes but should be considered carefully, especially since these were selected patients from a single center and the Achilles heel of bioprosthetic valves remains SVD, which usually occurs beyond 46 months.[20] Noteworthy, 54% of patients showed mild-moderate stenosis at last echocardiographic follow-up (34 ± 26 months).

Early mortality

Regarding early mortality, the observed differences between Ross (3.7%), mAVR (7.0%), and hAVR cohorts (10.6%) were substantial. The higher early mortality risk after paediatric mAVR and hAVR compared to the Ross procedure can be attributed mostly to the widely varying patient profiles across groups. Regarding haemodynamics, mAVR was more often performed in patients with isolated regurgitation compared to the Ross procedure and hAVR. The aetiology of valve dysfunction was more often related to endocarditis or rheumatic disease in mAVR than in Ross patients. Concomitant anomalies were comparable among Ross and mAVR patients. Compared to mAVR, previous cardiac interventions were more frequently performed in patients undergoing the Ross procedure or hAVR. Conversely, during AVR, the number of concomitant procedures and annular enlargement was higher during mAVR compared to Ross. Indeed, no conclusive evidence of selection bias was observed in our sensitivity analysis. However, unobserved patient selection may still be embedded in the decision-making process during valve selection, possibly reflecting in observed outcomes. For example, hAVR represents a last resort alternative for most surgeons, therefore forming a selected cohort. Survival has previously shown to be largely determined by patient-related factors, in addition to prosthesis type alone.[34]

A previous meta-analysis by our group in 2016[1] showed higher early mortality than the current analysis after mAVR (7.3%), hAVR (12.8%), and the Ross procedure in children (4.2%) and infants (16.9%). In a nationwide analysis between 2000–10, Brown *et al.*[35] reported a decreasing trend in 30-day mortality for paediatric cardiac surgery in general, although not evidently observed for Ross or non-Ross AVR procedures. Nelson *et al.* recently reported early mortality comparable to the current review in 3446 children undergoing AVR.[36]

Late mortality

Late mortality after Ross (0.5%/year), mAVR (1.0%/year), and hAVR (1.4%/year) in children varied greatly between groups. Microsimulation-based survival relative to the matched general population revealed that, in the first 20 years after the Ross procedure, survival was better (94.8% [95% CI: 93.3%–95.9%]) compared to mAVR (86.3% [95% CI: 83.5%–89.3%]). Better survival after the Ross procedure compared to mAVR corresponds with a nationwide report[37] and a propensity-adjusted comparison.[38]

Compared to the general population, all substitutes demonstrated impaired survival in children. Prosthetic AVR has previously shown to be associated with additional mortality that is not observed in the general population.[39–41] For the Ross procedure, this stands in contrast to earlier observations of survival in young adults. Studies revealed that the

Table 2 Pooled outcome estimates for all valve substitutes

	Ross procedure			Mechanical prosthesis			Homograft		
	Estimate (95%CI)	Heterogeneity	n	Estimate (95%CI)	Heterogeneity	n	Estimate (95%CI)	Heterogeneity	n
Early mortality (%)	3.72 (2.96–4.66)	$I^2 = 22.3\%$ ($P = 0.119$)	36	6.95 (5.05–9.56)	$I^2 = 16.1\%$ ($P = 0.274$)	15	10.55 (6.57–16.95)	$I^2 = 53.2\%$ ($P = 0.046$)	7
Early reintervention (%)	4.69 (3.34–6.58)	$I^2 = 34.6\%$ ($P = 0.070$)	19	4.20 (2.39–7.38)	$I^2 = 0.0\%$ ($P = 0.559$)	8	2.83 (0.93–8.63)[a]	$I^2 = 0.0\%$ ($P = 1.000$)	1
For bleeding (%)	3.54 (2.31–5.44)	$I^2 = 48.2\%$ ($P = 0.009$)	20	2.88 (1.46–5.68)	$I^2 = 0.0\%$ ($P = 0.717$)	8	0.47 (0.03–7.49)[a]	$I^2 = 0.0\%$ ($P = 1.000$)	1
Early pacemaker (%)	3.17 (2.34–4.30)	$I^2 = 0.0\%$ ($P = 0.831$)	16	3.37 (1.94–5.87)	$I^2 = 0.0\%$ ($P = 0.801$)	8	2.13 (0.31–14.80)[a]	$I^2 = 0.0\%$ ($P = 1.000$)	1
Early stroke (%)	0.76 (0.32–1.82)	$I^2 = 0.0\%$ ($P = 0.982$)	10	1.45 (0.55–3.83)	$I^2 = 0.0\%$ ($P = 0.994$)	6	0.52 (0.11–2.55)[a]	$I^2 = 0.0\%$ ($P = 0.991$)	3
Late mortality (%/yr)	0.51 (0.39–0.66)	$I^2 = 34.5\%$ ($P = 0.030$)	32	0.99 (0.64–1.51)	$I^2 = 49.0\%$ ($P = 0.017$)	15	1.38 (0.78–2.46)	$I^2 = 31.5\%$ ($P = 0.200$)	6
Cardiac (%/yr)	0.48 (0.34–0.66)	$I^2 = 24.9\%$ ($P = 0.125$)	26	0.63 (0.32–1.24)	$I^2 = 58.9\%$ ($P = 0.007$)	11	1.29 (0.74–2.25)	$I^2 = 4.8\%$ ($P = 0.369$)	4
Valve-related (%/yr)	0.32 (0.23–0.46)	$I^2 = 0.0\%$ ($P = 0.750$)	25	0.54 (0.28–1.04)	$I^2 = 32.7\%$ ($P = 0.146$)	10	0.68 (0.35–1.34)	$I^2 = 0.0\%$ ($P = 0.608$)	4
SUD (%/yr)	0.28 (0.18–0.44)	$I^2 = 0.0\%$ ($P = 0.682$)	24	0.20 (0.09–0.44)	$I^2 = 0.0\%$ ($P = 0.996$)	10	0.68 (0.35–1.34)	$I^2 = 0.0\%$ ($P = 0.608$)	4
Reintervention (%/yr)	3.42 (2.86–4.10)	$I^2 = 77.3\%$ ($P < 0.001$)	26	1.18 (0.76–1.83)	$I^2 = 40.9\%$ ($P = 0.076$)	11	4.78 (2.63–8.69)	$I^2 = 86.3\%$ ($P < 0.001$)	6
Aortic valve (%/yr)	1.30 (1.04–1.61)	$I^2 = 56.0\%$ ($P < 0.001$)	30	1.11 (0.72–1.70)	$I^2 = 51.8\%$ ($P = 0.015$)	13	4.56 (2.47–8.41)	$I^2 = 86.6\%$ ($P < 0.001$)	6
For SVD/NSVD	86.2%	–	30	68.8%	–	7	90.7%	–	5
Allograft (%/yr)	2.28 (1.84–2.83)	$I^2 = 69.4\%$ ($P < 0.001$)	27	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
For SVD/NSVD	73.2%	–	23	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
Endocarditis (%/yr)	0.37 (0.20–0.67)	$I^2 = 71.1\%$ ($P < 0.001$)	21	0.34 (0.20–0.56)	$I^2 = 0.0\%$ ($P = 0.924$)	13	0.34 (0.16–0.78)	$I^2 = 0.0\%$ ($P = 0.706$)	5
Thromboembolism (%/yr)	0.13 (0.07–0.24)	$I^2 = 0.0\%$ ($P = 0.537$)	10	0.42 (0.25–0.68)	$I^2 = 0.0\%$ ($P = 0.557$)	13	0.09 (0.01–0.64)[a]	$I^2 = 0.0\%$ ($P = 0.650$)	2
Valve thrombosis (%/yr)	0.19 (0.09–0.38)	$I^2 = 6.5\%$ ($P = 0.381$)	10	0.33 (0.20–0.55)	$I^2 = 0.0\%$ ($P = 0.942$)	14	0.11 (0.02–0.55)[a]	$I^2 = 0.0\%$ ($P = 0.846$)	3
TE/VT (%/yr)	0.19 (0.10–0.37)	$I^2 = 19.0\%$ ($P = 0.269$)	10	0.62 (0.42–0.92)	$I^2 = 2.8\%$ ($P = 0.419$)	13	0.11 (0.02–0.55)[a]	$I^2 = 31.1\%$ ($P = 0.235$)	3
Bleeding (%/yr)	0.09 (0.03–0.22)	$I^2 = 7.4\%$ ($P = 0.373$)	8	0.32 (0.18–0.56)	$I^2 = 0.0\%$ ($P = 0.615$)	12	0.09 (0.01–0.64)[a]	$I^2 = 0.0\%$ ($P = 0.650$)	2
CVA (stroke + TIA) (%/yr)	0.09 (0.03–0.24)	$I^2 = 4.3\%$ ($P = 0.393$)	7	0.43 (0.25–0.76)	$I^2 = 0.0\%$ ($P = 0.869$)	10	0.11 (0.02–0.55)[a]	$I^2 = 0.0\%$ ($P = 0.846$)	3
Stroke (%/yr)	0.09 (0.03–0.24)	$I^2 = 4.3\%$ ($P = 0.393$)	7	0.33 (0.17–0.63)	$I^2 = 0.0\%$ ($P = 0.810$)	10	0.11 (0.02–0.55)[a]	$I^2 = 0.0\%$ ($P = 0.846$)	3
Pacemaker implantation (%/yr)	0.26 (0.15–0.44)	$I^2 = 0.0\%$ ($P = 0.490$)	9	0.14 (0.01–2.21)[a]	$I^2 = 0.0\%$ ($P = 1.000$)	1	0.26 (0.07–0.89)[a]	$I^2 = 0.0\%$ ($P = 0.830$)	3

[a]Indicates a fixed-effects model was used during pooling.

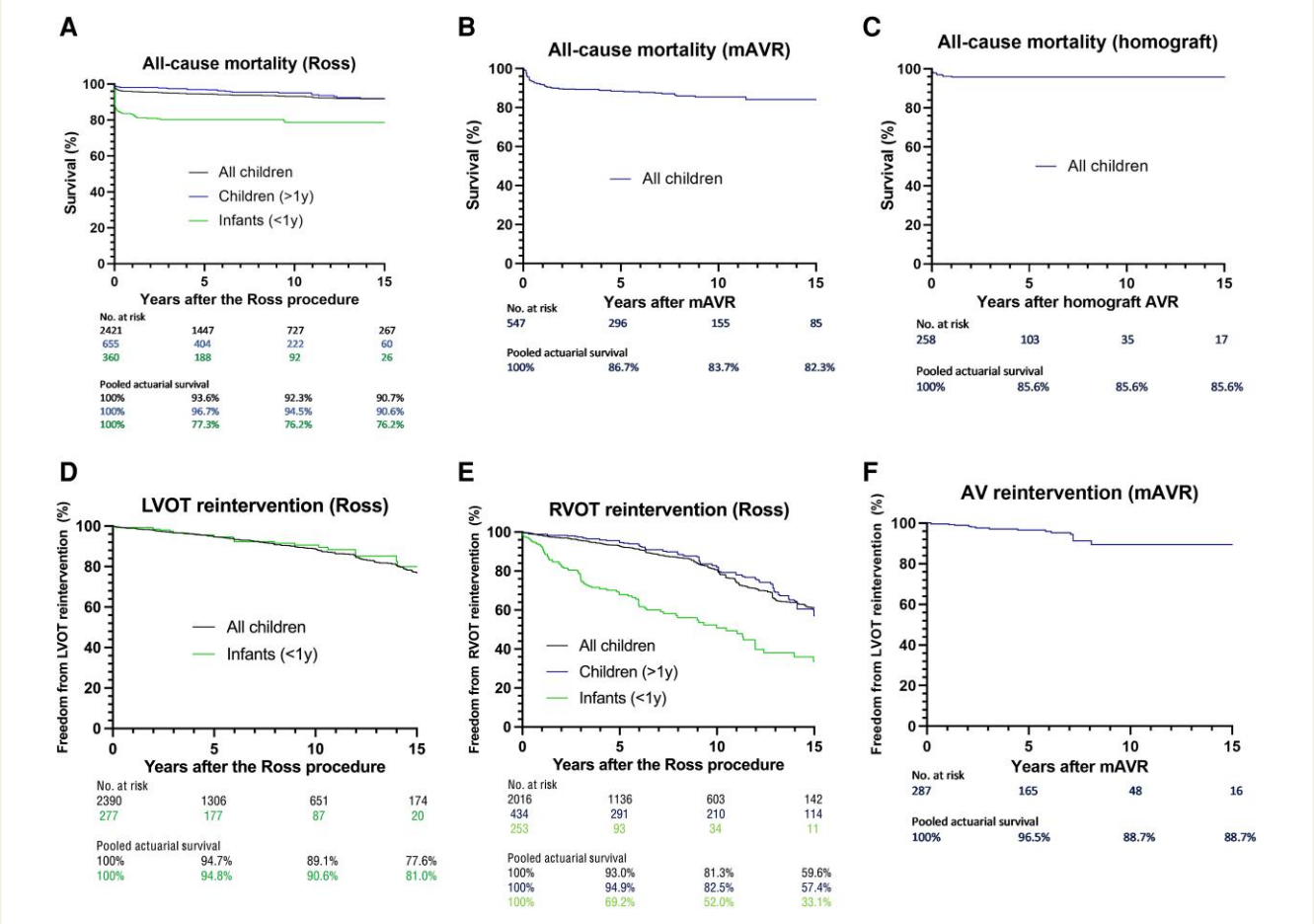


Figure 2 *A.* Pooled Kaplan–Meier freedom from all-cause mortality after the Ross procedure. *(B)* Pooled Kaplan–Meier freedom from all-cause mortality after mechanical AVR. *(C)* Pooled Kaplan–Meier freedom from all-cause mortality after homograft AVR. *(D)* Pooled Kaplan–Meier freedom from autograft (LVOT) reintervention after the Ross procedure. *(E)* Pooled Kaplan–Meier freedom from homograft (RVOT) reintervention after the Ross procedure. *(F)* Pooled Kaplan–Meier freedom from any aortic valve-related reintervention after mechanical AVR.

Ross procedure in adults actually yields a life expectancy comparable to the general population.[8,13] In children as opposed to young adults, relatively worse disease phenotype, higher early mortality and the hazard of multiple reinterventions early in life may contribute to the observed differences between our results and those in young adults, emphasizing that extrapolation of outcome in adults to children may not be justifiable for all outcomes.

Valve-related reintervention

All-cause reintervention was significantly lower after mAVR compared to Ross and hAVR (1.2%/year, 3.4%/year, and 4.8%/year, respectively). Occurrence rates of AV reintervention after the Ross procedure (1.3%/year) and mAVR (1.1%/year) differed slightly, while these rates were significantly lower compared to hAVR (4.6%/year). Microsimulation-based comparison of reintervention revealed that, when considering non-linear SVD/non-SVD (NSVD) occurrence and subsequent reinterventions, AV reinterventions at 20 years after a Ross procedure (42.0% [95% CI: 39.6%–44.6%]) were more common than after mAVR (17.8% [95% CI: 17.0%–19.4%]).

Importantly, the main causes for left-sided reintervention differ when reinterventions after a Ross, mAVR, and hAVR are compared. Where the commonest indication for reintervention after the Ross procedure is structural autograft deterioration,[38] reintervention after mAVR is mainly indicated due to the fact that children outgrow their prosthetic valve and that pannus formation occurs more often.[1,16,42] Indeed, microsimulation-based SVD/NSVD and reintervention rates after the Ross procedure were higher than after mAVR. Nevertheless, an important observation must be noted regarding the reoperative management of the failing autograft compared to mechanical prostheses. Whereas during reintervention after mAVR the valve itself cannot be repaired,[42] in the setting of autograft dilatation with or without insufficiency typically observed after a Ross procedure, a valve-sparing approach in children and young adults achieves good results and is increasingly performed.[43–46] Preservation of an autologous, nonthrombogenic valve may be of value in improving quality of life and clinical endpoints as our patients reach young adulthood.[47,48] Additionally, it has been suggested that a secondary Ross, performed after initial AV repair, is associated with improved survival and less reinterventions, although unmeasured confounders are conceivably at play.[49,50] Reinterventions after hAVR were often indicated as a result of early SVD compared to Ross and mAVR.[51,52]

The higher overall reintervention rate after the Ross procedure (3.4%/year) in comparison to mAVR (1.2%/year) was largely driven

Table 3 Microsimulation-based (event-free) life-expectancy and 20-year risks of valve-related morbidity

Valve substitute	Mechanical	Ross procedure	Ross procedure
Age group	<18 years	<18 years	<1 year
Mean age	13.0 ± 3.4 years	9.2 ± 5.6 years	96.3 ± 85.3 days
Life expectancy in first 20 postoperative years	17.0 (16.5–17.6)	18.9 (18.6–19.1)	16.9 (16.3–17.5)
Relative to matched general population	86.3% (83.5%–89.3%)	94.8% (93.3%–95.9%)	84.0%(81.1%–86.9%)
Event-free life-expectancy in 20 postoperative years	4.0 (3.6–4.4)	9.1 (8.7–9.4)	6.8 (6.4–7.1)
Twenty-year event risks, in %			
Autograft/aortic valve reintervention	17.8 (17.0–19.4)	42.0 (39.6–44.6)	29.1 (26.3–32.4)
Autograft/aortic valve SVD/NSVD	11.6 (9.2–13.7)	38.5 (33.8–42.0)	23.9 (16.6–28.1)
Pulmonary homograft reintervention	–	78.8 (75.6–82.2)	100 (97.5–100)
Pulmonary homograft SVD/NSVD	–	73.6 (67.0–78.0)	97.3 (90.3–100)
Valve thrombosis			
Autograft/aortic valve	6.1 (3.9–8.7)	2.4 (0.5–5.5)	2.3 (0.6–4.3)
Pulmonary homograft	–	2.2 (0.5–5.6)	1.7 (0.3–4.4)
Endocarditis			
Autograft/aortic valve	5.5 (2.9–10.0)	3.7 (1.7–6.6)	3.4 (1.3–6.0)
Pulmonary homograft	–	6.8 (3.5–12.9)	3.2 (1.3–6.9)
Cerebrovascular accident	8.0 (4.8–12.9)	1.9 (0.6–4.7)	2.0 (1.2–5.2)
Bleeding event	5.3 (3.0–8.6)	2.2 (0.6–4.8)	1.5 (0.4–3.9)
Simulation-based cause of death[a]			
Early postoperative mortality	31.6%	42.4%	79.4%
Background or excess mortality	32.0%	24.2%	3.2%
Mortality after reinterventions	10.4%	15.7%	9.6%

Values between brackets derived from the upper and lower boundaries of the 95% credible interval of the probabilistic sensitivity analysis.
[a] = percentage of total simulated mortality based on deterministic microsimulation of 10 000 individuals per group.

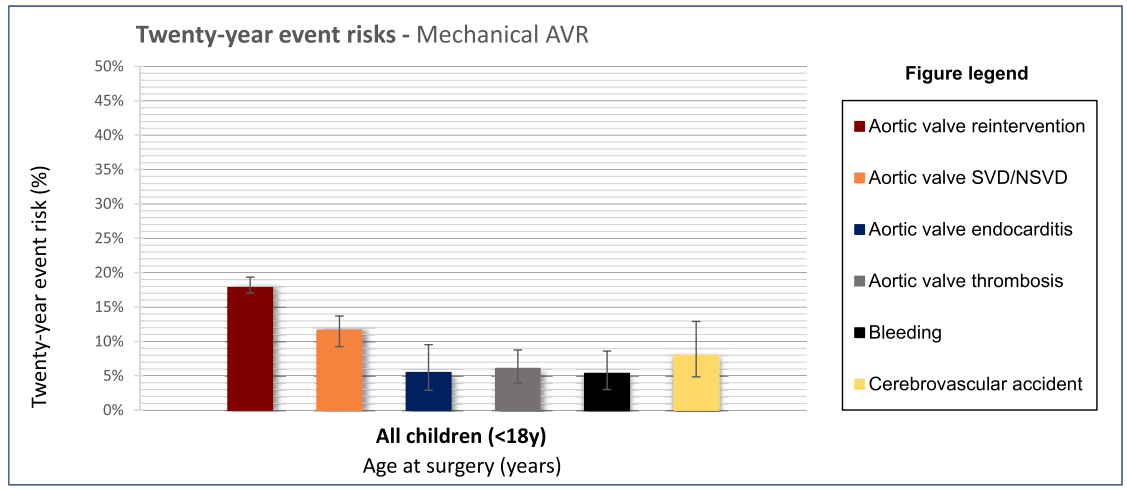
by homograft reinterventions. Homograft reinterventions after the Ross procedure in infants (6.5%/year) and children (2.3%/year) were high, as reflected in the microsimulation-derived reintervention risks. Pulmonary homograft deterioration in children is dependent on age and somatic growth and is considered a multifactorial process that is also affected by host immune responses and blood group incompatibility,[53,54] often resulting in stenosis.[55,56] Oversizing of the RVOT homograft may delay the need for re-replacement during childhood.[57,58] However, some controversy reigns in this regard as oversizing was not always shown to be protective of RVOT reintervention.[59]

Valve-related events

Bleeding, valve thrombosis, thrombo-embolism, endocarditis, SVD, and NSVD are valve-related complications that may occur after AVR. After the Ross procedure and mAVR, respectively, thrombo-embolic events, 0.1%/year (0.07%–0.2%/year) vs. 0.4%/year (0.3%–0.7%/year), and cerebrovascular accidents, 0.1%/year (0.03%–0.2%/year) vs. 0.4%/year (0.3%–0.8%/year), occurred significantly more frequently after mAVR. Also, after the Ross procedure compared to mAVR, there was a trend towards lower bleeding [0.1%/year (0.03%–0.2%/year) vs. 0.3%/year (0.2%–0.6%/year)] and valve thrombosis rates [0.2%/year (0.09%–0.4%/year) vs. 0.3%/year (0.2%–0.6%/year)]. After hAVR, pooled valve-related event rates except SVD were generally low although reported by little studies. Notably, after reconstructive, nonthrombogenic valve surgery like AV repair and the Ross procedure, rates of bleeding and thrombo-embolic complications are generally low.[11] The microsimulation revealed that, despite high rates of reinterventions after a Ross, the mean event-free life expectancy after a Ross [9.1 years (8.7–9.4years)] is considerably higher than after mAVR [4.0 years (3.6–4.4years)].

Functional status and quality of life

Most studies did not report pre- and postoperative Ross or NYHA classification. It has been shown that the Ross procedure, in adults, is associated with superior quality of life when compared with mAVR and equivalent quality of life when compared with valve repair.[60,61] Patients that underwent a Ross procedure, compared to mAVR, may face less anticoagulation-driven events over time that will likely influence their quality of life positively,[61] although being subject to a substantial reintervention hazard. Little is known about quality of life after AVR in children, especially in relation to valve-related events such as bleeding or reintervention. After mechanical mitral valve replacement, younger children show greater impairment in general health status than older



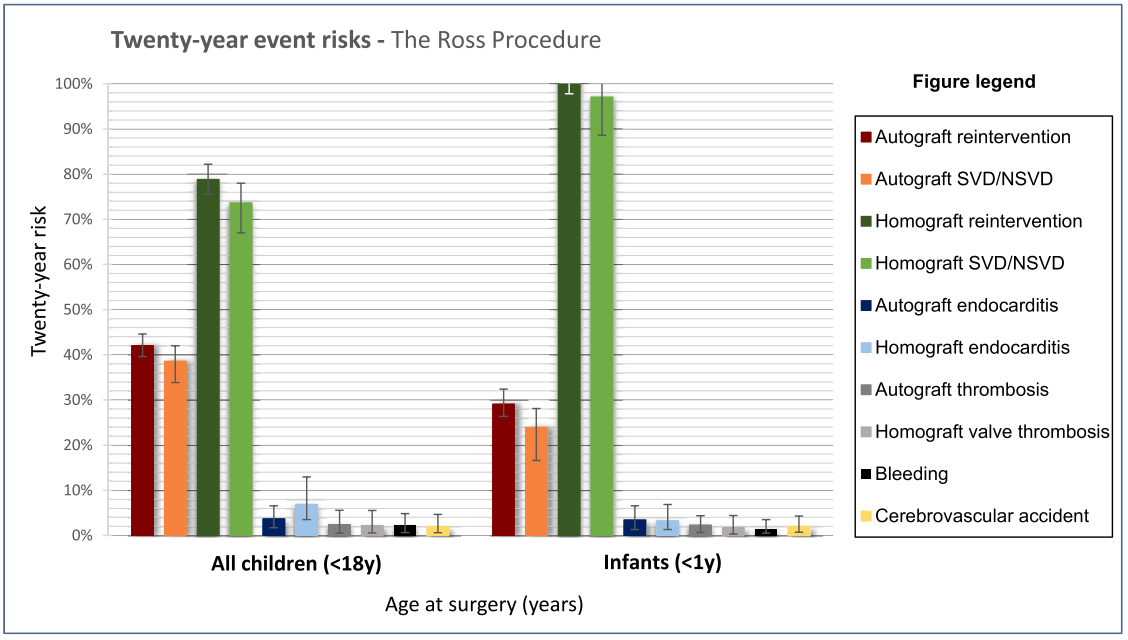


Figure 3 Microsimulation-based age-specific life expectancy and 20-year risks of valve-related morbidity after mechanical aortic valve replacement and the ross procedure. Included error bars represent 95% credible intervals. SVD indicates structural valve deterioration and NSVD indicates non-SVD.

children. Long-term anticoagulation treatment after mitral valve replacement was well tolerated in the majority of but not all patients. Sample size of this cross-sectional study, however, was limited to 19 children.[62]

As previously stressed by Etnel and colleagues,[11] the precise impact of these valve-related events on quality of life in children and adults, as opposed to length of life, remains to be investigated.

The Ross procedure in infants

Pooled mortality after the Ross procedure in infants was substantially higher (16.3%) than in children (3.7%). The course leading to early postoperative mortality in infants is typically characterised by preoperative need for mechanical ventilation and postoperative need for extracorporeal membrane oxygenation, probably reflecting poor ventricular function.[63]

Early mortality risks[64–68] and late overall reintervention rates[67,69,70] in our meta-analysis as well as in previous reports were high after the Ross procedure in infants, but generally low after AV repair in infants.[71–73] Taking these differences into account, one might argue that, whenever possible, adopting a strategy of initial repair followed by a delayed Ross later in childhood may improve outcome. It must, however, be acknowledged that patient selection likely played a role in the observed differences in early mortality between previous Ross and repair studies and that the Ross procedure simply may be the only viable option for several disease phenotypes.[74]

Somewhat counter-intuitively, autograft reintervention rates were lower for infants (1.0%/year) compared to children (1.3%/year). It has been theorised that this difference arises due to the relatively pronounced somatic growth these younger children are subject to, since in this setting, the autograft increases appropriately in diameter (i.e. in accordance with somatic growth) rather than pathologically (i.e. in

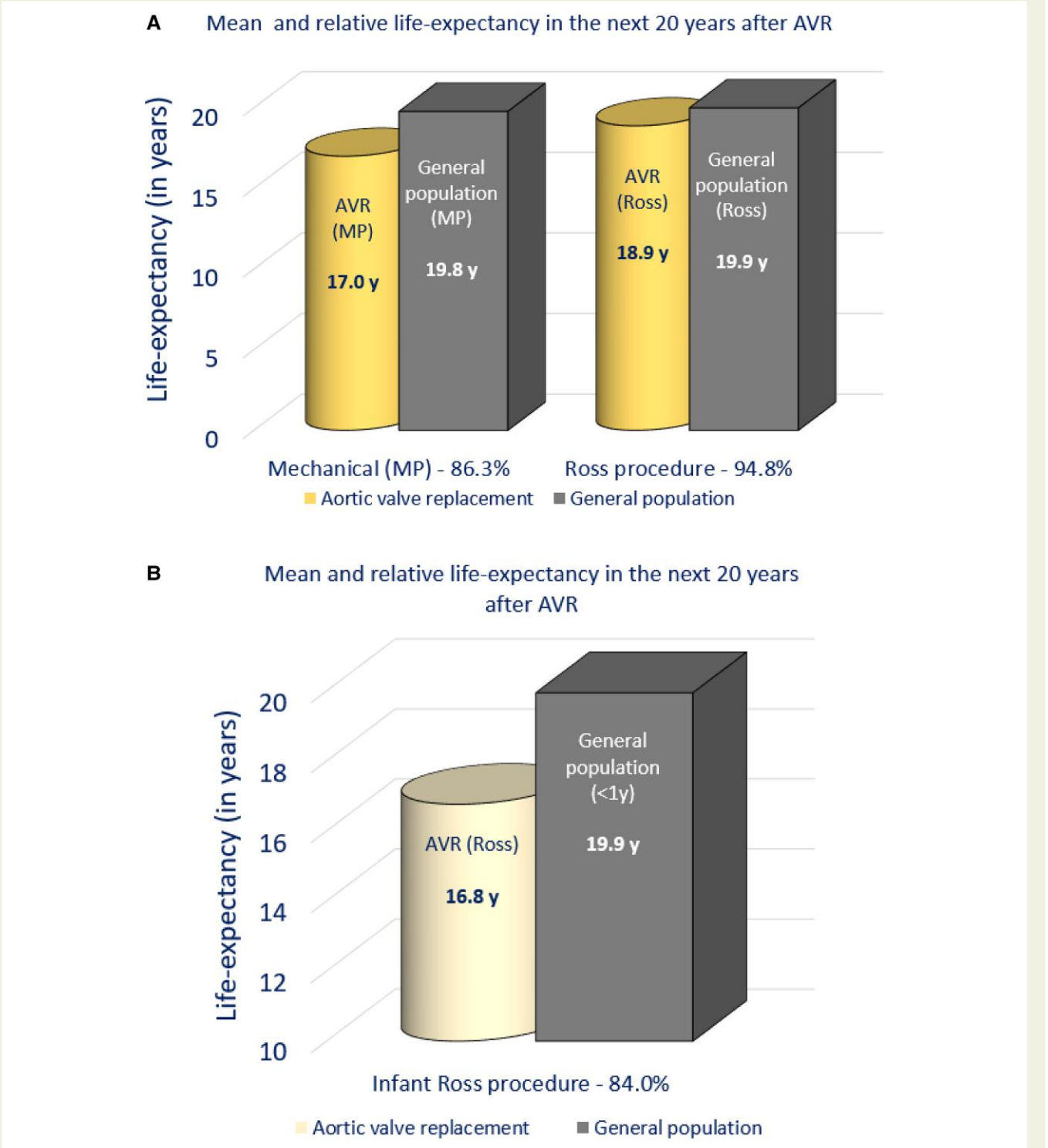


Figure 4 Microsimulation-based life expectancy after mechanical aortic valve replacement (<18 years) and the Ross procedure (<18 years and <1 year) compared with the age-, origin-, and sex-matched general population. Included error bars represent 95% credible intervals. *(A)* Life expectancy in children aged <18 years (Ross procedure and mechanical aortic valve replacement). *(B)* Life expectancy in infants aged <18 years at time of the Ross procedure.

the form of dilatation).[75–78] The autograft may also be less subject to immediate dilatation in infants because of exposure to higher pulmonary vascular resistance before autograft translocation.[79,80] Additionally, clinicians may be more hesitant towards a reintervention in infants already having undergone a Ross, since there are no attractive alternatives in growing children.

Particular difficulties arise when children present with complex LVOT obstruction, which may require additional annular

enlargement.[27,81] In this meta-analysis, children undergoing a Ross–Konno procedure were young, with numerous previous interventions and concomitant anomalies. Early (14.5%) and late mortality (1.7%/year) were high, as well as overall reintervention rates (11.0%/year). Some authors argue that infants with severe LVOT obstruction who are considered for a Ross–Konno are better off with a univentricular repair, either as a bridge to decision[82] or definitive,[83] although there is no evidence in support of these suggestions.

Three studies reporting clinical outcomes after an infant Ross addressed problems related to perioperative myocardial ischemia.[67,69,84] It has been hypothesised that these problems occur due to issues with the implantation of the right coronary button in the autograft.[85] Whether this technical challenge directly translates to higher postoperative mortality is not clear. Nevertheless, these studies did report a number of deaths confirmed[84] or suspected[67] to be attributable to the obstruction of coronary flow.

Strengths and limitations

To the best of our knowledge, this is the first systematic review using advanced methods of microsimulation and time-to-event meta-analysis after paediatric AVR. By assembling all the, often small, cohorts we obtained a large sample size, also including time-to-event data. This allows for a unique insight into real-world, long-term outcome after paediatric AVR with any of the available substitutes but does not aim to compare procedures directly.

Since this is a meta-analysis of retrospective studies, the limitations of pooling data from retrospective observational studies must be taken into consideration.[86] Second, selection bias of patients that were included in the studies might have influenced our outcomes due to the nature of observational studies, mainly relating to the fact that there is no randomization for allocation to treatment options. Risk of bias assessment revealed no serious implications for a single-arm meta-analysis with absolute risk estimates, i.e. exposure was ascertained through secure records (surgical records), all patients in each subgroup received the same treatment (Ross/mAVR/hAVR/bAVR), practices in studies reflect usual clinical practice, follow-up was long enough for outcomes to occur in most studies (5 years for late outcomes), and completeness of follow-up was adequate for almost all cohorts (>80%). Therefore, all studies were retained and risk of bias described (see *Supplement S1.3*). Other limitations include heterogeneity of underlying disease mandating treatment, practice variation patterns and biased choice of substitutes related to anatomical entities. Additionally, this systematic review only included studies with at least 20 participants in the meta-analysis, therefore missing out on literature reporting on smaller cohorts. Publication bias is possibly present, which might have influenced our results. The presence of possible publication bias was not explored with use of funnel plots since addressing publication bias in absolute risk outcomes, which are all of our outcomes, is associated with considerable methodological limitations that may give rise to funnel plot asymmetry.[87] Lastly, since extrapolation of event rates beyond the observed follow-up time may not be as appropriate in children as in adults, we decided to simulate the individual lives in our microsimulation for a period of 20 years. Hence, limited by the follow-up of included studies, no lifelong probabilities could be explored but only insights into early adulthood. The unavoidable assumption (given lack of data) of linear rates of valve-related events other than SVD/NSVD represents a limitation of the microsimulation.

Heterogeneity in studies may have introduced uncertainty in several reported outcomes. Nonetheless, due to the use of random-effects models, the uncertainty is integrated in the 95% confidence intervals used in our meta-analysis and the 95% CrI used in our microsimulation. Through univariable meta-regression (see *Supplement S12*), we obtained insights in possible sources of heterogeneity for a particular outcome. Still, heterogeneity of disease and in outcomes remain and represent limitations.

Implications for clinical practice and future perspectives

Decision-making in children with AVD remains a matter of numerous considerations pertaining to patient characteristics, valve durability, life-expectancy, anticoagulation prescription, pregnancy wishes, and patient and parent values. Throughout life, patients will face multiple decisions related to the treatment of their AVD. Accumulation of evidence on outcome after all potential therapies available may guide strategic valve intervention planning at a young age, also taking into account the potential options available for a second and third intervention. Ideally, while considering the best available evidence and unique characteristics of the individual patient is important, including patient values and goals in an informed decision-making with the patient and parents, is essential. Surgical technique and perioperative care have improved over the years and some improvements like autograft modifications and AV repair strategies[88,89] are still being made. Moreover, anticoagulation after mAVR shows room for improvement.[90] With optimal self-care in a developed country, mAVR yields excellent survival close to the general population in selected patients.[90]

Regarding outcomes after the Ross procedure, pooled data from the real world appear less encouraging than data from experienced, high-volume centres. The technically demanding nature of the Ross procedure likely contributed to the variation in reported outcomes that is potentially correlated with center- and surgeon volume.[91]

Focusing on survival, according to the microsimulation, it seems that survival after the Ross procedure in children, as opposed to adults, does not approximate life expectancy of the general population. Nonetheless, it appears that the Ross procedure in children provides a survival benefit over mAVR when compared to their age-matched, sex-matched and origin-matched general population. This is accompanied by avoidance of anticoagulation and the possibility to live a normal, active life. Contrarily, RVOT reinterventions were high after a Ross but these are generally associated with low mortality.[66,92] Concluding, the Ross procedure represents a unique option to children anticipating somatic growth, even to infants albeit with worse early outcomes.

Valve repair retains haemodynamic function and yields better quality of life than prosthetic AVR in adults.[60,61] Repair postpones AVR, which, especially in children where growth is anticipated, is desirable. Postponing a Ross at a young age may therefore be sensible if the valve is amenable to repair.[93,94] Improvements in repair techniques to achieve a durable result may thus be of benefit to children with AVD.[89,95–97]

Further modifications on the autograft,[98] improvements in AV repair[93,95] and other innovative therapies such as tissue-engineered valves[99,100] deserve attention in the future to further improve clinical and patient-reported outcome after paediatric AV surgery, not merely during childhood but beyond as well.

Conclusions

Based on current outcomes, results of paediatric AVR are suboptimal with substantial mortality especially in the very young, anticoagulation-

related morbidity after mAVR and considerable reintervention hazards after a Ross and other biological substitutes. Noteworthy, compared to the general population, the Ross procedure offers a survival benefit over mAVR (*Structured Graphical Abstract*). It is essential to carefully weigh pros and cons of different substitutes during valve selection in individual children.

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Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

All authors declare no conflict of interest for this contribution.

Data Availability

All data, analytic methods and study materials will be made available upon request.

Funding

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Ethical Approval

MEC-2021–0784.

PROSPERO Registration Number

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