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Aortic valve repair in neonates, infants and children: a systematic review, meta-analysis and microsimulation study

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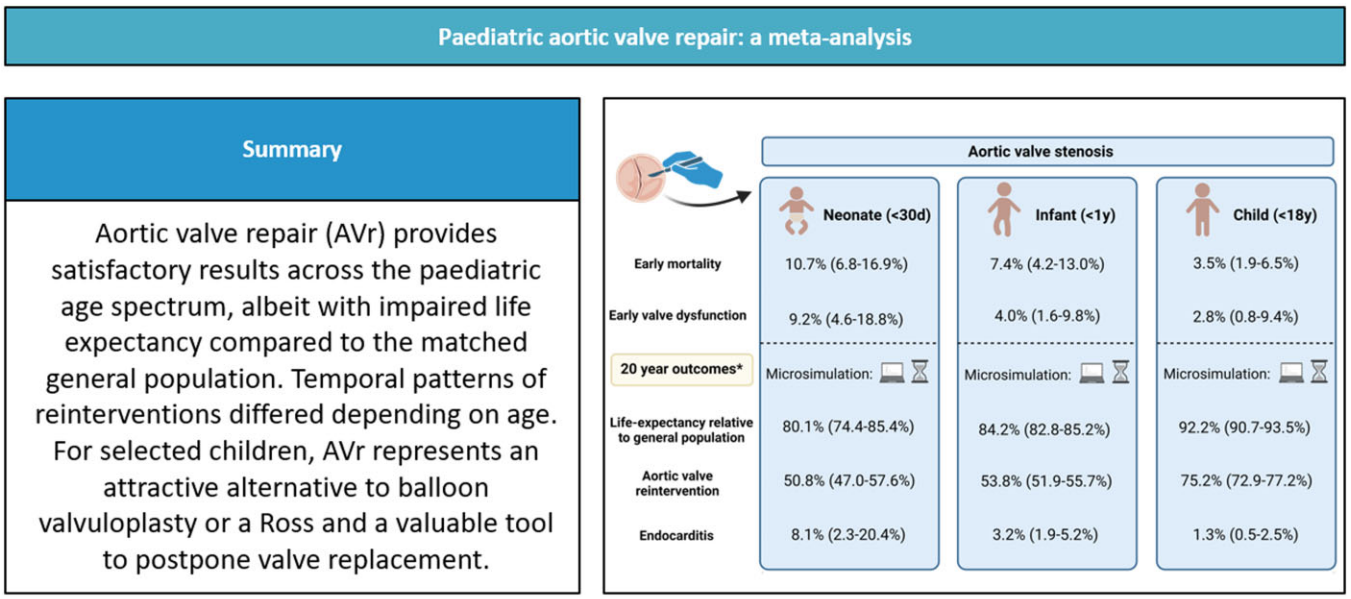


Legend: Summary of microsimulation-based outcomes after paediatric aortic valve repair for aortic stenosis across age groups.

Abstract

OBJECTIVES: To support clinical decision-making in children with aortic valve disease, by compiling the available evidence on outcome after paediatric aortic valve repair (AVr).

METHODS: A systematic review of literature reporting clinical outcome after paediatric AVr (mean age at surgery <18 years) published between 1 January 1990 and 23 December 2021 was conducted. Early event risks, late event rates and time-to-event data were pooled. A microsimulation model was employed to simulate the lives of individual children, infants and neonates following AVr.

RESULTS: Forty-one publications were included, encompassing 2 623 patients with 17 217 patient-years of follow-up (median follow-up: 7.3 years; range: 1.0–14.4 years). Pooled mean age during repair for aortic stenosis in children (<18 years), infants (<1 year) or neonates (<30 days) was 5.2 ± 3.9 years, 35 ± 137 days and 11 ± 6 days, respectively. Pooled early mortality after stenosis repair in children, infants

and neonates, respectively, was 3.5% (95% confidence interval: 1.9–6.5%), 7.4% (4.2–13.0%) and 10.7% (6.8–16.9%). Pooled late reintervention rate after stenosis repair in children, infants and neonates, respectively, was 3.31%/year (1.66–6.63%/year), 6.84%/year (3.95–11.83%/year) and 6.32%/year (3.04–13.15%/year); endocarditis 0.07%/year (0.03–0.21%/year), 0.23%/year (0.07–0.71%/year) and 0.49%/year (0.18–1.29%/year); and valve thrombosis 0.05%/year (0.01–0.26%/year), 0.15%/year (0.04–0.53%/year) and 0.19%/year (0.05–0.77%/year). Microsimulation-based mean life expectancy in the first 20 years for children, infants and neonates with aortic stenosis, respectively, was 18.4 years (95% credible interval: 18.1–18.7 years; relative survival compared to the matched general population: 92.2%), 16.8 years (16.5–17.0 years; relative survival: 84.2%) and 15.9 years (14.8–17.0 years; relative survival: 80.1%). Microsimulation-based 20-year risk of reintervention in children, infants and neonates, respectively, was 75.2% (72.9–77.2%), 53.8% (51.9–55.7%) and 50.8% (47.0–57.6%).

CONCLUSIONS: Long-term outcomes after paediatric AVr for stenosis are satisfactory and dependent on age at surgery. Despite a high hazard of reintervention for valve dysfunction and slightly impaired survival relative to the general population, AVr is associated with low valve-related event occurrences and should be considered in children with aortic valve disease.

Keywords: Aortic valve disease • Valve repair • Valve sparing • Paediatrics • Microsimulation

ABBREVIATIONS

AR	Aortic regurgitation
AS	Aortic valve stenosis
AV	Aortic valve
AVD	Aortic valve disease
AVr	Aortic valve repair
BV	Balloon aortic valvuloplasty
HR	Hazard ratio
KM	Kaplan–Meier
LV	Left ventricular
NYHA	New York Heart Association
RVD	Repaired valve dysfunction

INTRODUCTION

Congenital aortic valve stenosis (AS) represents ∼75% of all congenital obstructions of the left ventricular (LV) outflow tract [1] and commonly requires surgical management at some point during its course, although often effectively but temporarily relieved by balloon valvuloplasty [2, 3]. Due to percutaneous or surgical treatment, haemodynamics of the valve change as patients grow. Neonates and infants usually present with pure stenosis of the aortic valve (AV) and/or subvalvular LV outflow tract, whereas older children and young adults often exhibit a component of aortic regurgitation (AR) due to treatment and possible root dilatation, while in late adulthood, AS reoccurs in some patients as a result of degeneration and calcification of the valve [4].

Treatment decision-making in young children with AS poses a true dilemma [2, 3, 5]. Balloon aortic valvuloplasty (BV) offers an option to reduce AS in a minimally invasive setting [3], although varying degrees of AR are usually observed in due course given uncontrolled disruption of valve components [6, 7]. Surgical AV repair (AVr) has evolved significantly since its first application in 1956 and may more appropriately address the diseased AV compared to BV by enabling application of patient-tailored techniques under direct vision [8]. Low-thrombogenic, growth-adapting surgical alternatives such as AVr or a pulmonary autograft (Ross procedure) are preferred over prosthetic AV replacement by many surgeons, especially since this disease mandates lifelong management [9, 10]. Nevertheless, a haemodynamically satisfactory AVr result characterized by long-term durability is not easily accomplished in all patients [4, 8].

Over the past decades, AVr techniques in adults have substantially improved and are currently associated with low operative mortality and morbidity, along with a 10-year freedom from reintervention of ∼90% in experienced centres [11]. Techniques used in adult AV surgery have been increasingly applied in children given its potential advantages in the growing child [12]. Moreover, AVr yields excellent results in terms of quality of life in adults, appearing superior to mechanical AV replacement and yielding comparable QoL to patients after a Ross [13, 14].

Interest in paediatric AVr has grown and its current role in the treatment of aortic valve disease (AVD) is becoming established [8, 15, 16]. However, evidence regarding AVr in children is scattered across numerous reports that are often small in sample size with varying patient characteristics and outcomes. Furthermore, procedures are commonly performed by 1 or 2 surgeons in experienced centres, making outcomes difficult to generalize.

To support decision-making in paediatric patients with AVD, this study aims to systematically review published short- and long-term outcomes after surgical AVr for AR in children and congenital AS in neonates, infants and children and employ microsimulation to provide an outlook of long-term patient outcomes after AVr across age groups.

METHODS

Registration

The protocol for this systematic review and meta-analysis was registered in the PROSPERO registry (CRD42022292320) and approved by the local medical ethics committee of the Erasmus University Medical Centre (MEC-2022-0252). Informed consent was not obtained, as this study concerned a systematic review of published literature. This systematic review was reported in accordance with the updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Supplementary Material) [17].

Search strategy and study selection

On 23 December 2021, MEDLINE, Embase, Web of Science and Cochrane Library were searched by a biomedical information specialist using keywords related to surgical AVr in neonates,

infants, children and/or adolescents. The final search string is listed in Supplementary Material S1. Titles and abstracts were independently screened by 3 reviewers (Reda Rhellab, Nova van den Bogerd, Dominick Getrouw (non-author)) using the online Rayyan software [18]. Full-text screening was performed independently by 3 reviewers (Reda Rhellab, Nova van den Bogerd, Dominick Getrouw (non-author)) using the EndNote software, adhering to identical exclusion criteria. Inclusion criteria were observational studies or randomized controlled trials reporting on surgical, transaortic AVr considering at least 20 consecutive patients with a mean age <18 years (maximum age ≤21 years) published in or after 1990. Studies only focusing on patients with a hypoplastic aortic root, univentricular repair or a history of previous AV surgery and/or patients with pre-existing comorbidities such as connective tissue disease were excluded. Also, studies including only patients undergoing AVr after BV were excluded. If the full text of a publication was not available, it was obtained by applying for an interlibrary loan program established between universities.

Given the pooling of single-arm studies of limited sources in this meta-analysis, while adhering to strict inclusion and exclusion criteria, and describing the characteristics of the articles included as well as the patients included in the studies (summary of baseline characteristics), a formal quality analysis of the included manuscripts was not performed.

Data extraction

Microsoft Office Excel 2016 (Microsoft Corp., Redmond, WA, USA) was used for data extraction. Two reviewers (Maximiliaan L. Notenboom, Reda Rhellab) and one non-author (Dominick Getrouw), independently from each other, extracted all data. All extracted data were then verified by another reviewer (Maximiliaan L. Notenboom or Reda Rhellab), again independently from each other. In case of disagreement on any reported value, an agreement was reached through consensus. All recorded study characteristics, baseline patient characteristics, operative details and outcome measures are enclosed in Supplementary Material S1.

Definitions

Functional class before and after AVr was defined according to the New York Heart Association (NYHA) classification or the Ross classification for heart failure in children, as described by the study. Mortality and morbidity were documented according to the 2008 guidelines by Akins *et al.* [19]. Early outcome events were defined as events occurring within the first 30 days after AVr, and late outcome events as occurring after the first 30 days after AVr.

Studies were categorized according to (i) preoperative haemodynamic nature of AVD and (ii) age of the patients during AVr. Categories regarding AV haemodynamics included all repairs in children (<18 years), repairs for AR in children (<18 years) and repairs for AS in children (<18 years). Regarding age, subgroups were created within AS patients, namely for repairs for AS in children (<18 years), repairs for AS in infants (<1 year) and repairs for AS in neonates (<30 days). Baseline characteristics, surgical details and outcomes were pooled separately according to subgroup. A (sub)cohort was included in the AS or AR subgroup if all patients preoperatively exhibited isolated/predominant AS or isolated/predominant AR, respectively, as reported by the study.

Repaired valve dysfunction (RVD) was defined as residual (early) or reoccurrence (late) of at least moderate AS, AR or a combination of both, as reported by the authors. Reinterventions for RVD were documented separately as a subcategory of all AV reinterventions.

Statistical analyses

The statistical software used is described in Supplementary Material S1. Continuous variables are presented as mean ± standard deviation. Categorical variables are presented as counts and percentages. Occurrence rates (constant hazards) 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 and surgical characteristics were summarized by sample size weighting. Inverse variance weighting was carried out for the purpose of pooling event risks (early events), according to the number of patients, and event rates (late events), according to the number of follow-up patient-years. All outcomes were pooled on a logarithmic scale. The estimation of between-study variance was performed according to the Der Simonian and Laird method (random-effects model). In case an event (i.e. reintervention) did not occur in a study, it was assumed that 0.5 patients in this study had the event to enable statistical pooling (continuity correction). *P*-values <0.05 were considered statistically significant.

Estimates of reconstructed time-to-event data, derived from published Kaplan–Meier (KM) curves, were extracted and combined using the method described by Guyot *et al.* [20]. Details regarding the methodology are provided in Supplementary Material S1.

The Cochran-*Q* statistic and $\bar{i}^2$ statistic were used to assess the proportion of total heterogeneity attributable to between-study heterogeneity. Univariable random-effects meta-regression was performed to explore potential sources of heterogeneity in outcome measures. The effect of baseline characteristics and surgical details listed in Table 1, as well as median year of surgery on the outcomes of interest was investigated. Possible publication bias was explored by conducting a sensitivity analysis in which the quartile of studies with the smallest sample size was temporarily excluded from the analysis.

Microsimulation

Microsimulation models are capable of simulating lives of individual patients and take into account age-specific risks and hazards of valve-related events that may occur during the remaining life of a particular patient. A microsimulation model based on the 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 (Supplementary Material S1). The health states assumed in the model were alive and death. Since follow-up duration was too short to make inferences about lifetime risks, simulations were limited to the first 20 postoperative years.

All-cause mortality can be divided into deaths directly attributable to valve-related causes and deaths not directly attributable to valve-related causes. The latter consists of both background

Table 1: Baseline characteristics and surgical details after repair for aortic valve stenosis in children, infants and neonates

	Repairs for aortic valve stenosis		
	Children (<18 years) Pooled estimate	Infants (<1 year) Pooled estimate	Neonates (<30 days) Pooled estimate
Total number of patients	777	721	367
Follow-up			
Mean (years), mean ± SD	9.4 ± 2.2	5.8 ± 2.2	6.8 ± 2.3
Total, patient-years	6616	4148	2087
Age, mean ± SD	5.2 ± 3.9 years	35 ± 137 days	11 ± 6 days
Male, median (IQR)	68.9% (59.7–77.9)	74.2% (70.4–79.6)	75% (75.0–75.0)
Urgent, median (IQR)	54.6% (54.6–54.6)	62.1% (53.1–73.6)	100% (100.0–100.0)
Haemodynamics, median (IQR)			
Aortic stenosis	99.4% (96.7–100.0)	100% (100.0–100.0)	100% (100.0–100.0)
Aortic regurgitation	0% (0.0–0.0)	0% (0.0–0.0)	0% (0.0–0.0)
Combined	0.6% (0.0–3.3)	0% (0.0–0.0)	0% (0.0–0.0)
Unicuspid AV, median (IQR)	2.9% (0.0–3.3)	6.9% (0.0–30.0)	16.1% (0.0–27.8)
Bicuspid AV, median (IQR)	73.1% (65.2–82.9)	78.2% (64.2–85.9)	58.1% (46.2–66.7)
Etiology, median (IQR)			
Congenital	100% (100.0–100.0)	80.1% (0.0–100.0)	100% (100.0–100.0)
Congenital after BAV	1.2% (0.0–4.5)	0% (0.0–0.0)	0% (0.0–0.0)
Rheumatic	0% (0.0–0.0)	0% (0.0–0.0)	0% (0.0–0.0)
Endocarditis	0% (0.0–0.0)	0% (0.0–0.0)	0% (0.0–0.0)
Other/unknown	0% (0.0–0.0)	19.9% (0.0–100.0)	0% (0.0–0.0)
Concomitant anomalies, median (IQR)	45.5% (12.8–87.6)	79.4% (42.2–100.0)	88.1% (53.8–100.0)
Aortic anomalies	9.5% (0.0–20.6)	16.2% (3.1–24.5)	20.2% (0.0–34.6)
Aortic coarctation	7.3% (0.0–14.4)	14.7% (3.1–22.6)	12.2% (0.0–16.7)
Interrupted arch	0.7% (0.0–2.1)	0.5% (0.0–1.9)	1.2% (0.0–3.8)
Arch hypoplasia	1.5% (0.0–4.1)	1.2% (0.0–7.5)	4.9% (0.0–15.4)
Other/unknown anomalies	0% (0.0–0.0)	0% (0.0–0.0)	% (–)
Ventricular septal defect	2.6% (0.0–6.2)	8.4% (0.0–16.4)	6.7% (0.0–11.5)
Atrial septal defect	4.0% (0.0–6.2)	7.9% (5.0–11.3)	15.9% (0.0–35.0)
Transposition of the great arteries	0.0% (0.0–0.0)	0% (0.0–0.0)	% (–)
Subaortic stenosis	9.5% (0.0–23.7)	21.3% (0.0–60.0)	21.6% (0.0–36.1)
Endocardial fibroelastosis	8.1% (0.0–21.6)	14.0% (0.0–60.0)	20.9% (0.0–36.1)
Other/unknown anomalies	21.3% (7.5–69.6)	29.0% (10.8–70.0)	48.8% (16.7–84.6)
Previous cardiac intervention, median (IQR)	8.6% (4.5–11.3)	3.0% (0.0–10.0)	0.7% (0.0–3.8)
Aortic valve intervention	1.8% (0.0–8.7)	0% (0.0–0.0)	0% (0.0–0.0)
Percutaneous	1.8% (0.0–8.7)	0% (0.0–0.0)	0% (0.0–0.0)
Aortic valve repair	0% (0.0–0.0)	0% (0.0–0.0)	0% (0.0–0.0)
More than 1 previous AV procedure	0% (0.0–0.0)	0% (0.0–0.0)	0% (0.0–0.0)
Aortic surgery	3.7% (0.0–7.2)	2.4% (0.0–10.0)	3.9% (3.9–3.9)
Coarctectomy	2.7% (0.0–5.2)	2.4% (0.0–10.0)	3.9% (3.9–3.9)
VSD closure	1.6% (0.0–3.1)	0.3% (0.0–1.9)	0% (0.0–0.0)
Associated LVOTO surgery	0% (0.0–0.0)	0% (0.0–0.0)	0% (0.0–0.0)
Subaortic stenosis	0% (0.0–0.0)	0% (0.0–0.0)	0% (0.0–0.0)
Supravalvular stenosis	0% (0.0–0.0)	0% (0.0–0.0)	0% (0.0–0.0)
Other/unknown	3.2% (0.0–6.2)	1.0% (0.0–5.7)	1.5% (0.0–3.8)
Repair technique, median (IQR)			
Commissural repair	94.6% (0.0–100.0)	100.0% (100.0–100.0)	100% (100.0–100.0)
Only commissural	29.3% (0.0–100.0)	23.8% (0.0–98.4)	26.4% (0.0–100.0)
With cusp repair	32.5% (0.0–100.0)	44.6% (0.0–100.0)	61.1% (0.0–100.0)
Cusp repair	32.5% (0.0–100.0)	44.6% (0.0–100.0)	61.1% (0.0–100.0)
Only cusp repair	0% (0.0–0.0)	0% (0.0–0.0)	0% (0.0–0.0)
Cusp, commissure and annulus	0% (0.0–0.0)	0% (0.0–0.0)	0% (0.0–0.0)
Unknown combination	5.4% (0.0–1//00.0)	0% (0.0–0.0)	0% (0.0–0.0)
Subaortic stenosis resection, median (IQR)	3.3% (3.0–4.3)	2.7% (0.0–3.8)	2.6% (0.0–3.8)
Concomitant procedures, median (IQR)	16.7% (8.1–21.7)	29.1% (0.0–43.4)	42.1% (36.5–50.0)
Aortic surgery	4.0% (0.0–8.2)	12.8% (0.0–16.4)	18.4% (13.9–23.1)
Other valve surgery	0.4% (0.0–1.2)	1.3% (0.0–2.4)	0% (0.0–0.0)
Endocardial fibroelastosis resection	0.7% (0.0–4.3)	0% (0.0–0.0)	1.8% (0.0–3.8)
Other procedures	9.5% (5.8–13.0)	17.2% (0.0–35.9)	21.9% (9.6–34.6)

AV: aortic Valve; EFE: endocardial fibroelastosis; LVOTO: left ventricular outflow tract obstruction; SD: standard deviation.

mortality in the general population and excess mortality that does not directly result from valve-related events but is only observed after AVr. Methods to obtain the matched-background mortality are described in Supplementary Material S1. Excess mortality is expressed as a hazard ratio (HR) relative to the background mortality observed in the general population. Details of

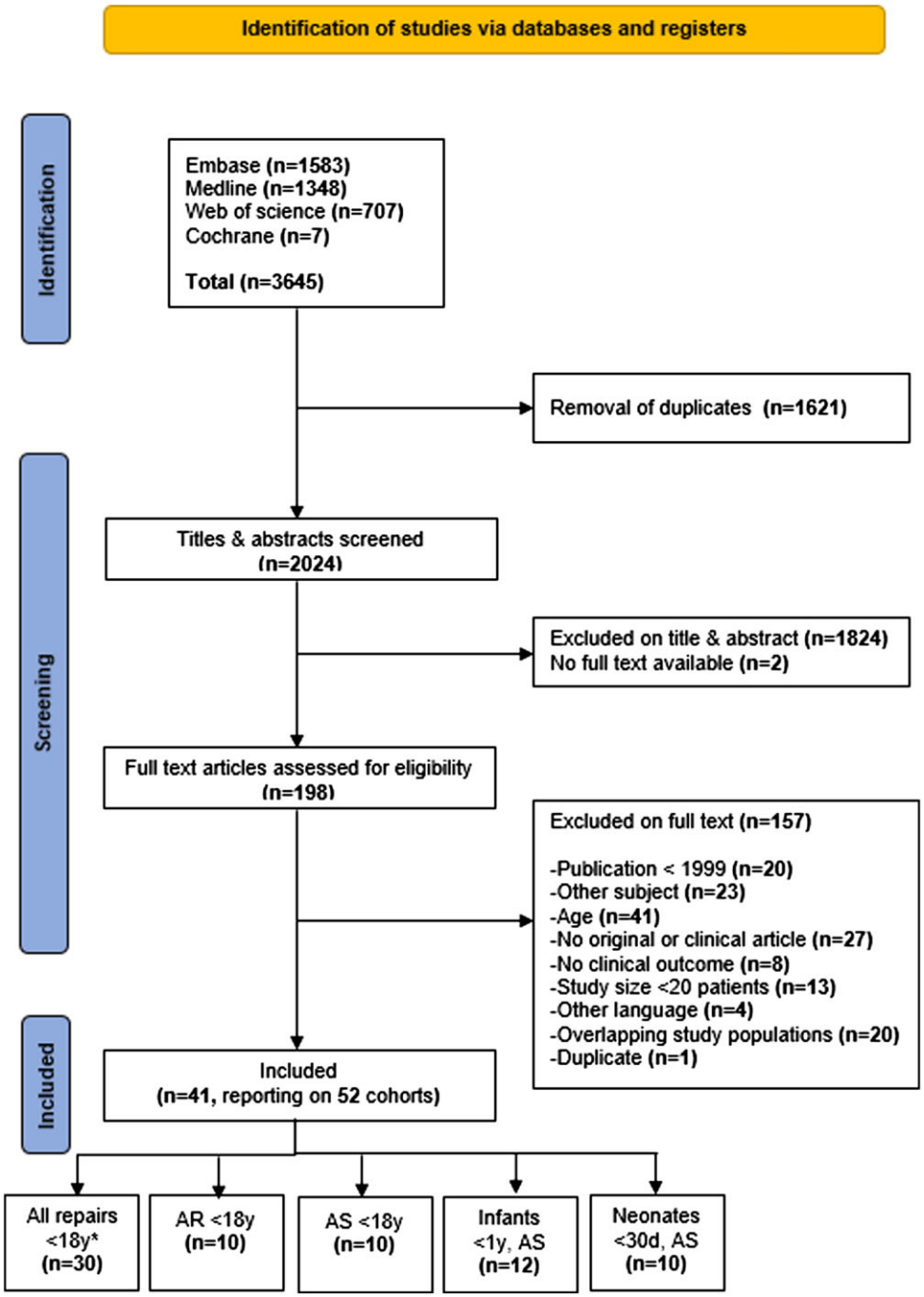


Figure 1: Flowchart of study selection. *The total number of publications ($n = 41$) includes 1 publication from which only Kaplan–Meier curves were used. Baseline characteristics and outcome estimates of these publications are not provided due to overlapping populations with other publications included in this meta-analysis.

the excess mortality estimation are listed in Supplementary Material S1.

The hazards of all-cause AV reintervention and RVD were assumed to be time-varying and were modelled by fitting flexible parametric survival models to the pooled time-to-event data (Supplementary Material S2). No time-to-event data were available for other events (endocarditis, stroke, thrombo-embolism, bleeding, valve-thrombosis); thus, constant hazard rates were assumed for these events.

To obtain age-specific estimates of life expectancy and 20-year risks of valve-related morbidity after AVr for AS, the microsimulation simulated cohorts of 10 000 patients for each of the age groups (<30 days, <1 year and <18 years), of whom 75.0%, 74.2% and 68.9% were male, respectively (pooled male/female percentages). For AR,

this simulation was performed for 10 000 patients <18 years (65.6% male).

Probabilistic sensitivity analysis was performed to consider uncertainty in the input parameters of the microsimulation (Supplementary Material S1). Internal validation of late survival and reintervention was assessed by plotting microsimulation events and observed events of the KM meta-analysis.

RESULTS

Study selection

In total, 2024 publications were identified by the systematic literature search, of which 41, all observational studies, were included in the meta-analysis (Fig. 1), yielding a total of 2623 patients with 17 217 patient-years of follow-up. The median follow-up among studies was 7.3 years, ranging from 1.0 to 14.4 years. Individual study characteristics of included studies are listed in Supplementary Material S6 (references in Supplementary Material S3).

Meta-analysis

Baseline patient characteristics and surgical details of children, infants and neonates undergoing AVr for AS are summarized in Table 1. The complete table, including the number of studies per variable, is listed in Supplementary Material S4. Age-specific pooled preoperative, early postoperative and late postoperative peak systolic AV gradients for AS patients are plotted in Fig. 2. Baseline characteristics and surgical details for all repairs (<18 years), repairs for AS (<18 years) and repairs for AR (<18 years) are summarized in Supplementary Material S7.

Pooled risks of early outcomes and pooled occurrence rates of late mortality and late valve-related events are listed in Table 2 for children, infants and neonates with AS. The complete table, including heterogeneity, is listed in Supplementary Material S5. Pooled outcomes after all repairs, repairs for AS and repairs for AR (Supplementary Material S8) and individual study outcome estimates (Supplementary Material S9) are enclosed in the Supplementary Material. Weights of individual studies for each outcome of interest are given in Supplementary Material S10. Pooled outcome after isolated commissurotomy (± cusp thinning) without additional AV procedures is provided in Supplementary Material S11.

Summarized across 6 studies reporting postoperative NYHA functional class at last follow-up after AVr (median follow-up: 6.4 years; range: 1.7–10.0 years), 99.7% of the patients were in NYHA class I or II.

Age- and disease-specific pooled KM curves of survival, freedom from AV reintervention and freedom from AV replacement are presented in Fig. 3A–C. The median time to AV reintervention was 13.0 years after AVr for AS and 7.7 years after AVr for AR, both <18 years. Pooled KM curves for survival and reintervention after isolated commissurotomy are provided in Supplementary Material S12. A reconstructed KM presenting freedom from AR ≥ moderate following AVr for AS and AR is provided in Supplementary Material S13.

Microsimulation

Simulated risks of valve-related morbidity and survival are presented in Fig. 4 (events) and Fig. 5 (life expectancy) and listed in Supplementary Material S14. Calibration of the microsimulation model is shown in Supplementary Material S15 for all subgroups. The mean event-free life expectancy in the first 20 years after AVr for AS was 6.9 years (95% credible interval: 6.6–7.3 years) and after

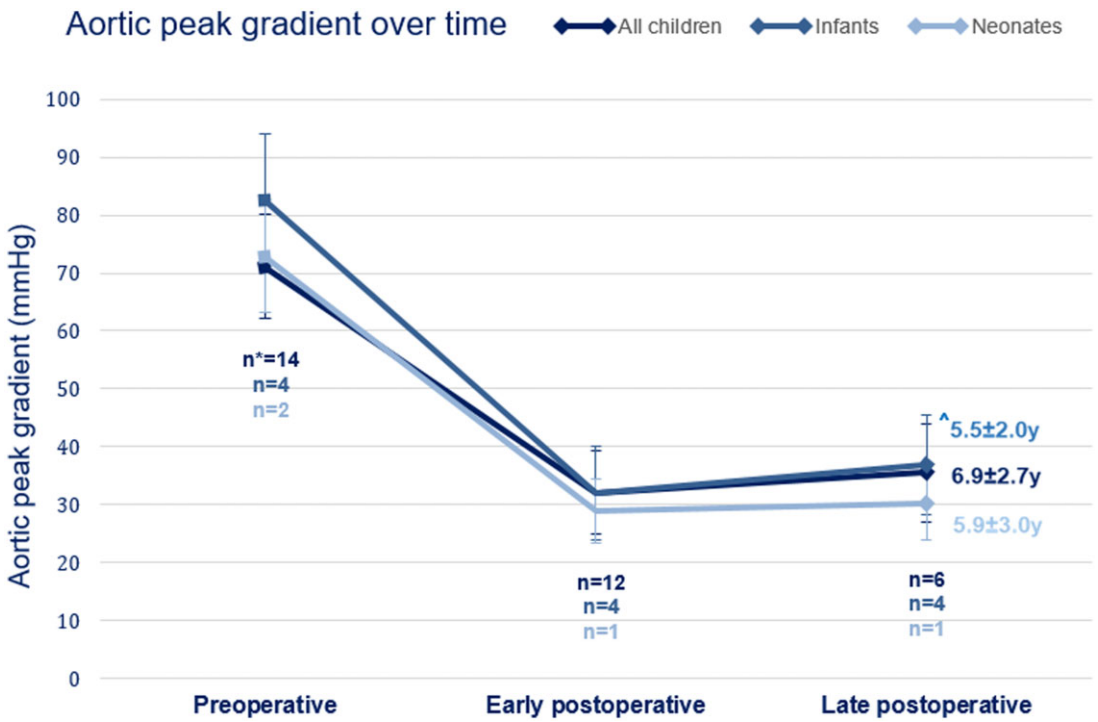


Figure 2: Evolution of aortic valve peak gradient (mmHg) on preoperative, early postoperative and late postoperative echocardiographic studies for children, infants and neonates with AS. *n = number of studies, ^mean echocardiographic follow-up per subgroup.

Table 2: Pooled early and late outcomes after repair for aortic valve stenosis in children, infants and neonates

	Pooled estimate (95% CI)		
	Repairs for aortic valve stenosis		
	Children (<18 years)	Infants (<1 year)	Neonates (<30 days)
Early mortality (%)	3.48 (1.87–6.47)	7.35 (4.16–12.98)	10.72 (6.79–16.93)
Early reintervention for bleeding (%)	0.81 (0.32–2.03)	2.05 (0.96–4.37)	1.64 (0.48–5.60)
Early repaired valve dysfunction (%)	2.78 (0.82–9.44)	3.98 (1.61–9.83)	9.24 (4.55–18.78)
Requiring early reintervention (%)	0.73 (0.31–1.75)	1.34 (0.62–2.87)	2.22 (0.93–5.28)
Early endocarditis (%)	0.77 (0.22–2.63)	1.26 (0.44–3.56)	1.53 (0.50–4.69)
Early pacemaker (%)	0.90 (0.26–3.09)	1.52 (0.31–7.45)[a]	–
Early stroke (%)	0.73 (0.21–2.49)	1.23 (0.46–3.25)	1.51 (0.53–4.27)
Late mortality (%/year)	0.50 (0.29–0.87)	1.63 (0.96–2.77)	1.50 (0.71–3.15)
Cardiac (%/year)	0.40 (0.23–0.71)	1.50 (0.78–2.89)	1.26 (0.55–2.85)
Valve related (%/year)	0.25 (0.15–0.44)	0.84 (0.31–2.31)	0.66 (0.23–1.86)
SUD (%/year)	0.19 (0.09–0.39)	0.32 (0.13–0.78)	0.37 (0.13–1.05)
Reintervention (%/year)	3.36 (1.70–6.65)	8.40 (5.53–12.75)	6.57 (3.24–13.35)
Aortic valve (%/year)	3.31 (1.66–6.63)	6.84 (3.95–11.83)	6.32 (3.04–13.15)
For repaired valve dysfunction (%)	98.7	98.0	100.0
Percutaneous (%/year)	0.40 (0.21–1.23)	1.52 (0.62–3.76)	0.48 (0.18–1.28)
Surgical (%/year)	2.76 (1.39–5.49)	5.65 (3.78–8.45)	4.58 (2.91–7.20)
Re-repair (%)	14.7%	32.7%	24.9%
Re-replacement (%)	51.2%	42.1%	62.9%
Ross procedure (%)	20.1%	25.4%	43.5%
Mechanical prosthesis (%)	26.7%	7.7%	18.0%
Other/unknown (%)[b]	34.1%	25.2%	12.2%
Endocarditis (%/year)	0.07 (0.03–0.21)	0.23 (0.07–0.71)	0.49 (0.18–1.29)
Thromboembolism (%/year)	0.10 (0.02–0.47)[a]	0.14 (0.02–0.96)[a]	0.38 (0.05–2.76)[a]
Valve thrombosis (%/year)	0.05 (0.01–0.26)[a]	0.15 (0.04–0.53)	0.19 (0.05–0.77)
TE/VT (%/year)	0.10 (0.02–0.47)[a]	0.16 (0.01–2.54)[a]	–
Bleeding (%/year)	0.08 (0.02–0.31)	0.17 (0.02–1.24)[a]	0.17 (0.02–1.23)[a]
CVA (stroke + TIA) (%/year)	0.08 (0.02–0.41)[a]	0.13 (0.03–0.64)[a]	–
Stroke (%/year)	0.06 (0.02–0.20)	0.17 (0.06–0.48)	0.29 (0.09–0.88)
Pacemaker implantation (%/year)	0.05 (0.01–0.27)[a]	0.11 (0.03–0.43)	0.19 (0.03–1.34)[a]

[a]A fixed-effects model was used.

[b]Includes bioprosthesis aortic valve replacement, homograft aortic valve replacement and apico-aortic conduit insertion.

CI: confidence interval; CVA: cerebrovascular accident; SUD: sudden, unexplained death; TE: thrombo-embolism; TIA: transient ischaemic attack; VT: valve thrombosis.

AVr for AR, it was 5.5 years (5.3–5.8 years). The limited event-free life expectancy was driven by a high risk of AV reintervention in the first 20 years [75.2% (72.9–77.2) for AS, 78.8% (76.8–81.0) for AR]. The HR for excess mortality relative to the background mortality for children with AR and AS was 5.3 and 6.6, respectively. For neonates, it was 19.0 until they reached the age of 2, thereafter decreasing to 3.9. For infants, it was 54.0 until they reached the age of 2, thereafter decreasing to 1.0 (Supplementary Material S16).

For a neonate undergoing AVr, relative life expectancy compared to the matched general population was 80.1% (95% credible interval: 74.4–85.4%) and risk of AV reintervention was 50.8% (47.0–57.6%) in the first 20 postoperative years. For an infant undergoing AVr, relative life expectancy compared to the matched general population was 84.2% (82.8–85.2%) and risk of AV reintervention was 53.8% (51.9–55.7%) in the first 20 postoperative years. For a child (mean age 5.2 years, range 0–18 years) undergoing repair for AS, relative life expectancy compared to the matched general population was 92.2% (90.7–93.5%) and risk of AV reintervention was 75.2% (72.9–77.2%) in the first 20 postoperative years. For a child (mean age 9.9 years, range 0–18 years) undergoing repair for AR, relative life expectancy compared to the matched general population was 94.2% (93.3–94.9%) and risk of AV reintervention was 78.8% (76.8–81.0%) in the first 20 postoperative years.

Sensitivity analyses

Pooled estimates remained largely unchanged during sensitivity analyses (by temporarily excluding the smallest quartile of studies). For early outcomes, changes ranged from 0.19% to 0.32% and for late outcomes, changes ranged from 0.0%/year to 0.31%/year (Supplementary Material S17).

Heterogeneity

Considerable heterogeneity was observed for several outcomes after AVr. Individual estimates of the univariable random-effects meta-regression for all outcomes after AVr stratified by age (neonates, infants, children with AS) and haemodynamics (children with AS, children with AR) are listed in Supplementary Material S18.

DISCUSSION

Paediatric AVD mandates lifelong management, but lifelong surgical solutions do not exist. Over a lifetime, strategic planning of treatments should allow the greatest proportion of children to live a life as long as possible with good quality of life, while keeping in mind to minimize the risks and hazards of valve-related morbidity.

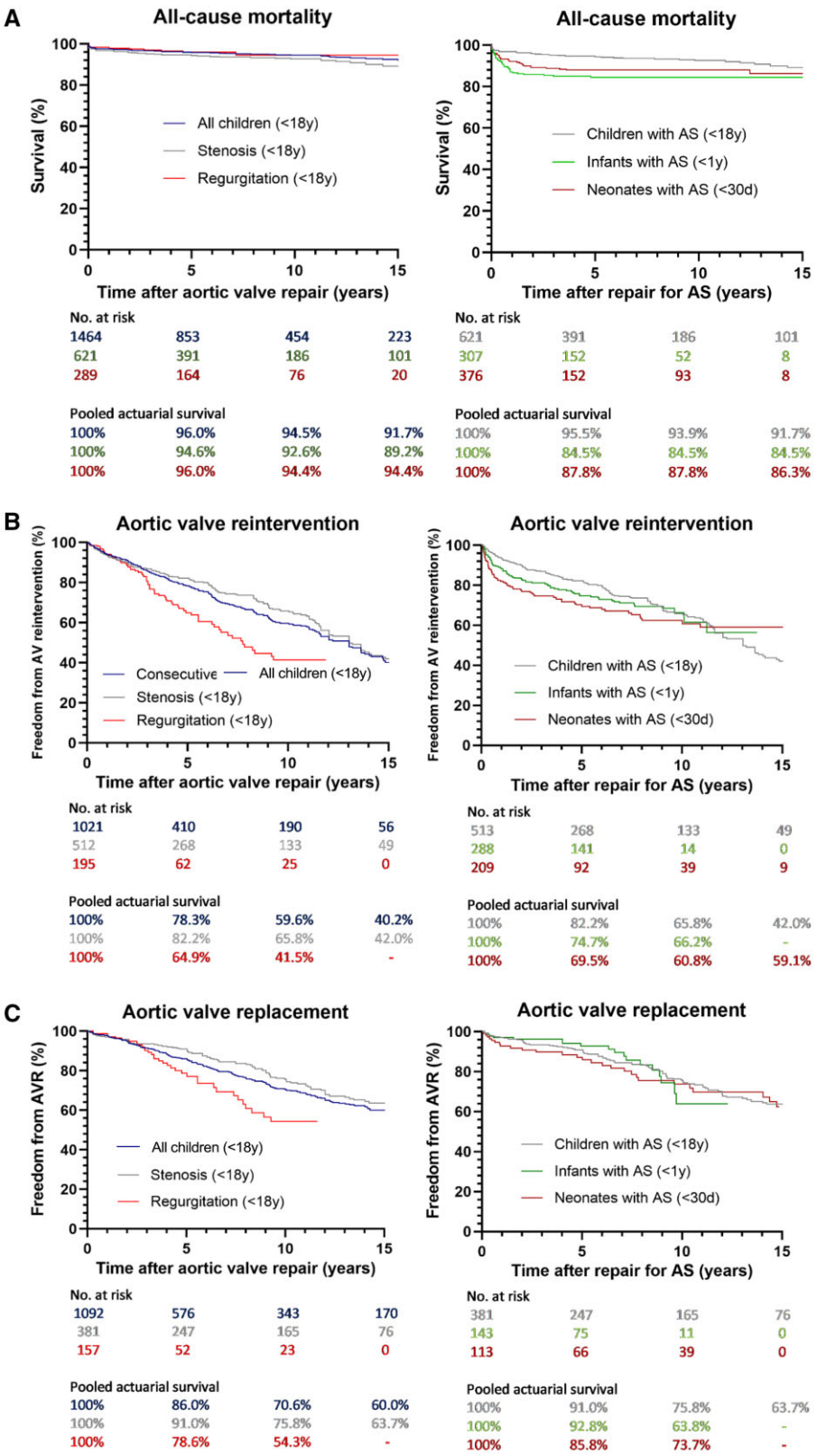
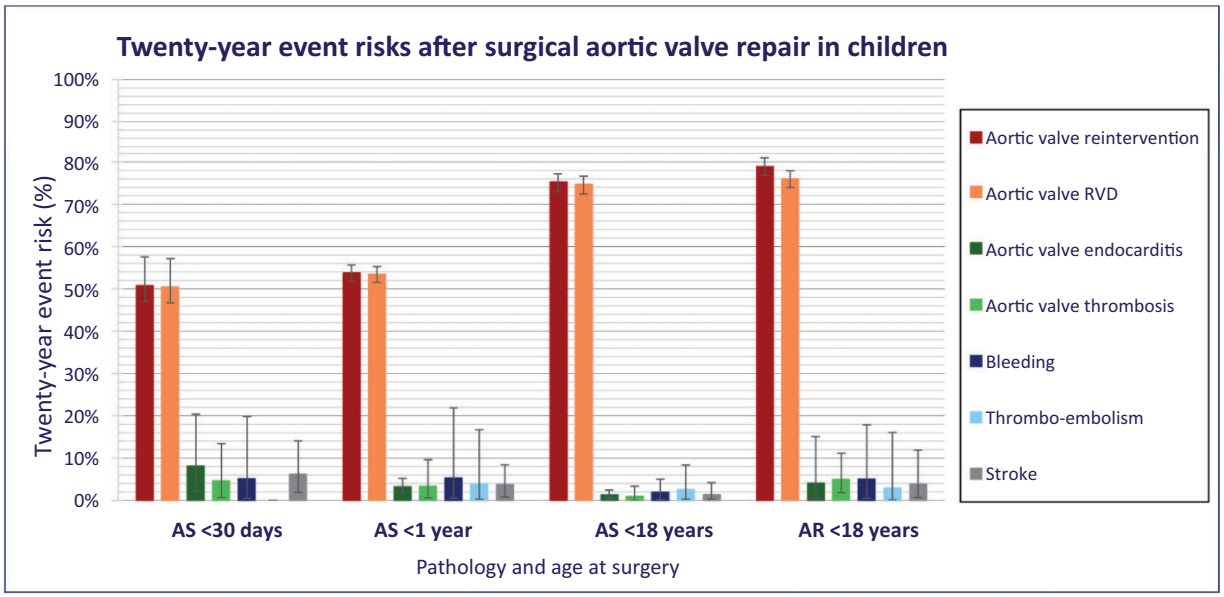
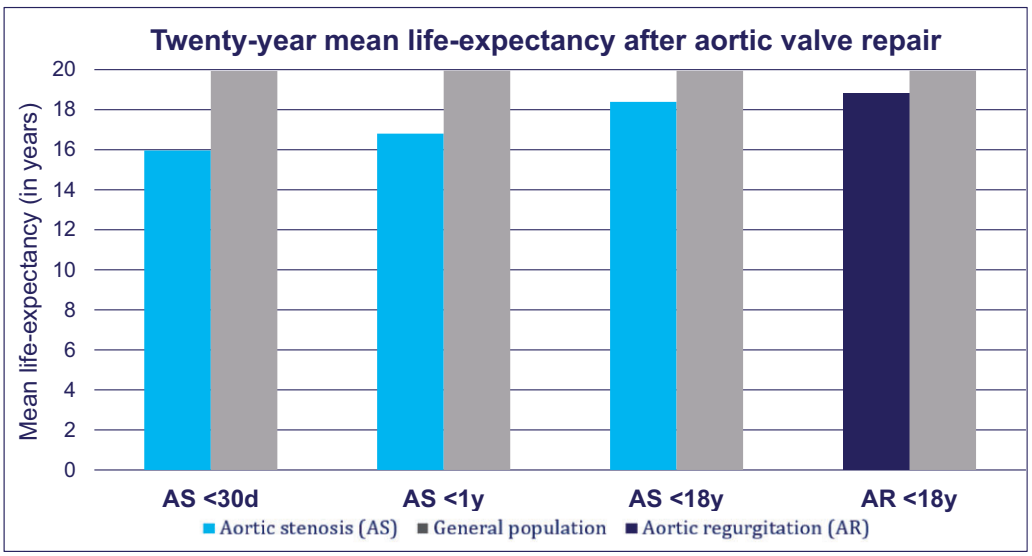


Figure 3: (**A**) Left: pooled Kaplan–Meier freedom from all-cause mortality after all aortic valve repairs, aortic valve repair for AS and aortic valve repair for AR. Right: pooled Kaplan–Meier freedom from all-cause mortality after valve repair for AS in children <18 years, AS in infants <1 year and AS in neonates <30 days. (**B**) Left: pooled Kaplan–Meier freedom from aortic valve reintervention after all aortic valve repairs, aortic valve repair for AS and aortic valve repair for AR. Right: pooled Kaplan–Meier freedom from aortic valve reintervention after valve repair for AS in children <18 years, AS in infants <1 year and AS in neonates <30 days. (**C**) Left: pooled Kaplan–Meier freedom from aortic valve replacement after all aortic valve repairs, aortic valve repair for AS and aortic valve repair for AR. Right: pooled Kaplan–Meier freedom from aortic valve replacement after valve repair for AS in children <18 years, AS in infants <1 year and AS in neonates <30 days.



AR, Aortic regurgitation; AS, Aortic stenosis; RVD, Repaired valve dysfunction.

Figure 4: Microsimulation-based age-specific life expectancy and 20-year risks of valve-related morbidity after aortic valve repair for AR (<18 years) and AS (<18 years, <1 year and <30 days). Included error bars represent 95% credible intervals. RVD indicates repaired valve dysfunction.



AR, Aortic regurgitation; AS, Aortic stenosis.

Figure 5: Microsimulation-based life expectancy after repair for AR (<18 years) and AS (<18 years, <1 year and <30 days) compared with the age-, origin- and sex-matched general population. Included error bars represent 95% credible intervals.

This is the first study investigating outcomes following AVr in children, using systematic review with meta-analysis and employing time-to-event data and advanced microsimulation to obtain a unique insight into long-term outcome for different age groups and disease phenotypes. Long-term outcome after AVr in this study was satisfactory and characterized by low rates of endocarditis, thrombo-embolic and bleeding events, despite a high reintervention hazard for all types of AVD across all ages. Long-term survival was slightly impaired in older children compared to the general population, while it was significantly impaired in infants and neonates. Through the microsimulation, it became clear that reintervention on the AV was required in ~75% of children under 18 years during the first 20 years postoperatively, regardless of haemodynamic diagnosis and that this was mainly driven by RVD. Early and late mortality were high in infants and neonates, but freedom from reintervention was better and freedom from replacement was comparable to older children. These results provide important insights into patient outcome for different age groups with AS or AR.

Early outcome

Alike early mortality after a Ross procedure [21–24], early mortality after AVr in neonates (10.7%) and infants (7.4%) was substantially higher than in children with AS (3.5%). The between-study variability was substantial, which may be explained by variation in incidence of hypoplasia of left-sided structures or concomitant mitral valve disease. Regarding indications, repairs for AS (3.5%) and AR (1.5%) exhibited different early mortality risks. Patient characteristics differed and mainly age was lower in patients with AS, which is a known risk factor for perioperative mortality [25].

Early reinterventions were uncommon and most often performed as a result of bleeding (1.2%) or repair dysfunction (1.5%). It should be noted that, according to the present analysis, a considerable number of children with preoperative AS (2.1%) as well as AR (9.7%) are being discharged with at least moderate AS and/or AR. In infants (2.7%) and neonates (8.0%) with AS, this was also observed. One could imagine that this was accepted as a part of the decision-making process for certain patients, for example, given the importance of postponing AV replacement. Nonetheless, these observations underscore the room for improvements in patient selection and surgical innovations, such as novel techniques, materials and devices and intraoperative evaluation of AVr success [26–28].

Late mortality

For children, infants and neonates undergoing repair for AS, respectively, pooled late mortality rates were 0.5%/year, 1.6%/year and 1.5%/year. For children undergoing repair for AR, late mortality was 0.6%/year. Compared to the age-, sex- and origin-matched general population, this translates to a microsimulation-based relative survival compared to the matched general population ranging from 80.1% in neonates to 92.2% in older children with AS and 94.2% in older children with AR.

Pooled late mortality comprises directly valve-related, background and excess mortality. In addition to low rates of bleeding and thrombo-embolic events, mortality after valve-related events was low. As the HR for excess mortality relative to the background mortality was high (AR: 5.3, AS: 6.6) for all subgroups undergoing AVr, it is reasonable to believe that causes other than background mortality or mortality directly related to valve-related causes contributed to mortality after AVr. These findings have led us to conclude that, to a great extent, mortality after AVr resulted from excess mortality, which is not a direct result of documented valve-related causes. Microsimulation revealed that the causes of death in older children mainly consisted of background or excess mortality (73.8% of all deaths at 20 years), whereas deaths ascribed to the index procedure or a reintervention, respectively, comprised 15.9% and 10.3% of all deaths within 20 years. Excess mortality was relatively high and a possible explanation for this observation may lie in the perioperative acceptance of suboptimal haemodynamic results, potentially leading to long-term LV pressure (i.e. due to recurrent/residual AS) or volume overload (i.e. due to recurrent/residual AR). In neonates with AS and children with AR, early RVD was frequent (neonates with AS: 9.2%, children with AR: 11.7%). These consequences of poor valve competence put patients at risk for ventricular failure and arrhythmias [29], which can be fatal and thus result in a higher excess mortality. According to our meta-analysis, some 40% of late deaths in children with AS or AR was sudden and unexplained. These deaths are not directly related to documented valve-related events but may represent a derivative of impaired AV function. This is supported by recent literature, which shows that residual lesion severity predicts worse survival after AVr [30]. Myocardial abnormalities in patients with (residual) AS may also play a role as it may cause an increase in extracellular volume fractions and ventricular dysfunction [31]. In patients with a reduced LV function preoperatively, it normalizes in most patients after AVr [32]. Pre-existing LV dysfunction, myocardial composition or endocardial fibroelastosis was not reported by the majority of studies but should be considered to investigate their association with postoperative outcomes, especially after BV [33]. Prevalence of endocardial fibroelastosis here ranged from 8% in older children to 20% in neonates. However, it is difficult to infer how these parameters affected outcomes as their relation with outcomes could not be taken into consideration.

In the second natural history study conducted in 1993 [29], more than half of all deaths in AS patients were sudden and unexplained, which is slightly higher than in the current study (AS: 38%, AR: 58%). The current study suggests that there may be a source of mortality not directly related to valve-related events, which should be further evaluated by longitudinal, prospective studies after AVr, also including echocardiographic data.

Repaired valve dysfunction and valve-related reintervention

Durability after AVr for AS is reportedly lower than durability observed after autograft valve replacement [34, 35]. However, AVr may be a valuable tool to postpone AV replacement in selected children.

Reinterventions on the AV were mainly indicated as a result of RVD (94.6%), regardless of age. We did however find that the 20-year microsimulation-based risk estimates of reintervention differ between age groups. Besides worse disease phenotype leading young children to present early, underlying causes for the higher reintervention hazard in young children during the first postoperative years include that restoring a well-functioning AV is more technically demanding, somatic growth is more pronounced, and a suboptimal result may be accepted more quickly in infants. Follow-up in most studies was short and the hazard for reintervention was highest in the first postoperative years (Fig. 3B). The microsimulation-based observations indicate that infants and neonates had lower 20-year reintervention risks compared to older children, likely the result of a greater competing risk of mortality in young children and the stabilization of reintervention hazard after 10 years, possibly due to decreasing somatic growth with time.

Microsimulation-based predictions showed that, after repair for AS or AR in children, risk of reintervention at 20 years was ∼75–80% and for neonates and infants with AS, this was ∼50–55%. Temporal patterns differed based on age, as we found a high hazard of reintervention for neonates and infants in early years that stabilized as time passed (∼10 years). Similarly, patients with AR exhibited significantly greater hazards of reintervention, starting from 3 years after AVr. These temporal patterns are essential to take into account for each patient. Importantly, freedom from any AV replacement at 10 years was ∼73.0% in all age groups with AS. The meta-analysis revealed that reinterventions most commonly included a re-repair, Ross procedure or mAVR, respectively, in 21.1%, 37.0% and 24.6% of reinterventions in

children. In infants and neonates, respectively, re-repair comprised 32.7% and 24.9% of reinterventions, further avoiding the need for replacement. Pooled analyses revealed that 64.0% of all AV replacements after AVr were performed with a Ross, further avoiding the need for anticoagulation and preserving a native, living valve.

Deciding between AVr and a Ross procedure to treat native AVD includes the trade-off whether the benefit of postponing AV replacement at a young age outweighs the increased hazard of valve dysfunction and subsequent reinterventions after AVr. A lifelong perspective is warranted, taking into account survival, growth potential, reintervention hazards, types of reinterventions, occurrence of valve-related events, parent/patient values and wishes in life, and quality of life. Importantly, we have learned that AVr is a valuable tool that buys time in the spirit of postponing AV replacement as long as possible, which should be the intention given recent insights [36].

Other valve-related complications

Valve-related events other than RVD and reintervention were uncommon. AVr for AS seldom requires use of patches, translating to low occurrence rates of endocarditis, thrombo-embolism, and bleeding after AS repair in children. Similarly, valve-related complications were low in neonates and infants with AS. Multiple reports have confirmed a low incidence of valve-related morbidity after AVr [37, 38]. A trend towards higher incidence of endocarditis and stroke in AR patients compared to AS patients was found in the microsimulation. A potential cause for this difference rests in the more widespread use of cusp-oriented AVr in AR (96.1%) compared to AS (32.5%) and, therefore, often use of patches, although no causality can be assumed here. Wallace *et al.* [39] concluded that in one-third of children, AVr could be achieved without use of a patch. When AV phenotype dictates patch use in children with unicuspid AV, some encourage not to use additional material covering >30% of cusp size [40].

Neonates and infants

The AV involved in critical AS is different from AS treated later in life [41, 42]. A small aortic root, thickened leaflets, hypoplastic interleaflet triangles, incompletely liberated commissures and loss of significant opening characterize the obstruction involved in critical AS [42]. Decision-making in young children remains difficult and the ideal treatment unidentified as it depends on centre, patient and disease-related factors. If a depressed LV function is present in critical AS, a combination of gentle BV to alleviate the LV while minimizing the risk of AR, followed by AVr within the next month yields promising results [7, 41]. If LV function does not improve, these patients may be palliated towards a single-ventricle trajectory (pulmonary banding, ductus stenting, Norwood).

The Ross procedure is considered the golden standard for children requiring AV replacement [9, 10, 24]. A neonatal Ross carries high mortality and is typically reserved as a last resort option for unrepairable AVs [23, 43]. Interestingly, a secondary Ross after a primary AVr yields superior survival and freedom from reintervention compared to a primary Ross, although unmeasured confounders are likely at play [44]. Therefore, it may be sensible to perform AVr in the selected neonate or infant with AS, to both delay AV replacement and improve Ross outcomes. Children undergoing AVr consist of a selected cohort. Anatomic characteristics, among others the presence of pliable cusps and the absence of severe subaortic stenosis [4], form a reason to assume the feasibility of AVr over AV replacement. Additionally, a substantial number of patients embedded in published AV replacement cohorts were likely considered for AVr at first. Treatment selection in infants remains complicated, particularly in those appearing candidates for both options—i.e. in the absence of multilevel obstructions requiring a Konno—where surgeons are not sure about the longevity of AVr.

Implications for clinical practice and future perspectives

The position of AVr compared to BV and Ross within the treatment of AVD is crucial to determine. Valve repair in older children, although performed in selected patients, is associated with lower early and late mortality compared to mechanical and homograft AV replacement in children [10]. Compared to Ross, which is the only valve substitute providing optimal life expectancy, these risks were comparable [10, 24]. Indeed, reintervention hazards after AVr were greater compared to primary AV replacement [24]. Nonetheless, AVr can be utilized as a tool to postpone AV replacement while recapitulating normal AV physiology and not posing severe additional risks for the patient. BV is an acknowledged treatment modality for congenital AS and there is an ongoing debate on whether it is superior to surgical AVr in young patients [3]. Importantly, practices vary between centres. In the current era, AVr may provide a better individualized approach for selected patients by more accurately aiming for native AV preservation while restoring haemodynamics [43, 45]. In this meta-analysis, re-repair was performed in 32.7% of all infants undergoing reintervention after AVr for AS. After BV, concerns have been raised regarding the possibility for re-reparative management [43, 46], given uncontrolled disruption of valve components. Observational data suggest that AVr achieves superior outcome compared to BV in young children in terms of reinterventions [6, 41] while comparable survival was reported [2, 3]. A recent propensity score matched study [16], however, showed no differences between BV and AVr in clinical outcomes including reinterventions. In a centre where both approaches were equally applied, freedom from AV replacement was comparable between BV and AVr [7]. In patients with a tricommissural result after AVr, evidence has accumulated in favour of AVr compared to BV [6, 41]. On the other hand, for example in unicommissural, unicuspid AVD, BV appears an attractive first strategy even to experienced surgical centres, with no surgical reinterventions in the first year after BV when performed in infancy [47]. Conversely, others suggest AVr for asymmetric valves by noting that BV could lead to unpredictable ruptures in such AVs, precluding future valve-sparing surgery [41]. Concluding, the debate is ongoing and the treatment choice should depend on the specific circumstances of the patient. For patients and their parents, it is important to weigh risks and benefits of all options and discuss them with a cardiologist and surgeon to make an informed decision. Practice variation and unmeasured confounders are at play given lack of randomized data comparing options. Microsimulation provides a valuable tool when comparing treatment alternatives by modelling lives of individuals that are prone to undergoing multiple interventions during a lifetime, while also at risk for other valve-related complications and background mortality.

A recent meta-analysis by our group investigating clinical outcome following the Ross procedure [24] showed comparable early mortality risks (3.7% vs 3.5%), late mortality rates (0.51%/year vs 0.50%/year) and reintervention rates (3.42%/year vs 3.36%/year) compared to AVr for AS, but patient characteristics varied significantly between the Ross and AVr populations, complicating comparisons.

For regurgitant AVD, the treatment decision-making trade-off lies between AVr and a paediatric Ross rather than BV. Comparisons between these alternatives are complex, mainly given little data on AVr for AR, little data on a paediatric Ross for AR and variability in patient characteristics between the 2 treatment groups. Concluding, both procedures are effective in the treatment of AVD and yield their own unique drawbacks and benefits, which should be tailored to the individual, typically older, child with AR. The method and optimal timing of surgery for paediatric AR remain a challenge [48].

Novel insights into AVr techniques have led to a structured approach to valves amenable to repair [8]. Thorough debridement with resection of nodular fibrosis, opening of fused commissures, leaflet thinning and carving of new interleaflet triangles enable surgeons to more appropriately address the stenotic AV than sole commissurotomy. In regurgitant valves, triangular leaflet plication, resuspension of free edges of prolapsing leaflets and raphe resection to mobilize the largest leaflet allow for a tailored approach to creating a competent AV [8]. Cusp extension is sometimes unavoidable [45]. When addressing AVD in children below 10 years, use of patches has shown to be associated with early reoperation and suboptimal results. Decision-making between a paediatric Ross and AVr should also consider the amount of additional tissue required for AVr. The search for the preferred leaflet repair material is still ongoing [49].

Neocuspidization has gained popularity, expanding to the paediatric population in more recent years [50]. In AVr strategies considering a neotricuspidization of the AV (e.g. Ozaki), occlusion of coronary ostia could occur in small patients since supranormal effective and geometric heights are required to effectuate coaptation and prevent incompetence [47]. Caution should be taken before routinely offering the Ozaki repair to younger patients and studies with long-term follow-up are warranted.

Strengths and limitations

This study is the first systematic review employing advanced methods of microsimulation and time-to-event meta-analysis in paediatric AVr. A large sample size in combination with advanced modelling approaches by subgroup provides an unprecedented insight into patient-specific outcome across the paediatric age spectrum.

First, limitations of pooling data from retrospective, nonrandomized studies must be taken into consideration [51]. Second, selection bias might have influenced pooled outcomes, as a abstracts and conference presentations were not included. Third, sensitivity analyses revealed that eventual publication bias did not substantially affect our outcomes. Publication bias was not explored with use of funnel plots since addressing publication bias in absolute risk outcomes is associated with methodological limitations that may give rise to funnel plot asymmetry [52]. Due to insufficient input data, we did not use microsimulation for patients with combined AS/AR. However, in spite of combined AS/AR in some children, most surgical repairs for these patients are tailored towards relief of the most predominant AV lesion (AS or AR). Little studies described how many patients with AVr for AS presented directly after BV, making it difficult to draw inferences on outcome after BV. Another limitation of meta-analysis includes the inability to answer very specific but relevant research questions, such as outcome after reoperative AVr versus primary AVr. Additionally, no competing risk analyses were performed in the meta-analysis. Contrarily, the microsimulation-based estimates do account for the competing risk of death. Meta-analytic estimates assume proportionality of hazards, which may not be correct for all events. Freedom from >2+ AR was calculated using time-to-event approaches, which carries statistical limitations over repeated measurement analysis in such data. Lastly, as little data were present on events other than reintervention, some credible intervals were large. Nonetheless, the message that valve-related events occur infrequently while reinterventions occur frequently remains clear.

Heterogeneity may have introduced uncertainty in reported outcomes. However, due to the use of random-effects models, this uncertainty is integrated into the 95% confidence intervals of the meta-analysis and the 95% credible intervals of the microsimulation. Sources of heterogeneity were also evaluated (Supplementary Material S11).

CONCLUSIONS

Summarizing, AVr provides satisfactory results across the paediatric age spectrum, albeit with impaired survival compared to the general population and sudden, unexplained death as an important contributor to excess mortality. The temporal pattern of reinterventions due to RVD differs depending on both age and haemodynamic nature of the disease at index surgery. For selected children with AS or AR, AVr represents an attractive alternative to BV or a primary Ross and is a valuable tool to postpone AV replacement. Improvements in patient selection and AVr techniques may improve outcomes by better identifying the repairable AV and decreasing excess mortality.

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SUPPLEMENTARY MATERIAL

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DATA AVAILABILITY

The data underlying this article will be shared on reasonable request to the corresponding author.

Author contributions

Maximiliaan L. Notenboom: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Software; Validation;

Visualization; Writing—original draft; Writing—review & editing. **Reda Rhellab:** Data curation; Methodology. **Jonathan R.G. Etnel:** Conceptualization; Formal analysis; Investigation; Methodology; Supervision; Visualization; Writing—review & editing. **Nova van den Bogerd:** Data curation; Formal analysis; Methodology; Software; Writing—review & editing. **Kevin M. Veen:** Conceptualization; Formal analysis; Investigation; Methodology; Software; Supervision; Visualization; Writing—review & editing. **Yannick J.H.J. Taverne:** Conceptualization; Data curation; Investigation; Supervision; Visualization; Writing—review & editing. **Willem A. Helbing:** Conceptualization; Supervision; Validation; Visualization; Writing—review & editing. **Pieter C. van de Woestijne:** Conceptualization; Formal analysis; Methodology; Supervision; Visualization; Writing—review & editing. **Ad J.J.C. Bogers:** Conceptualization; Investigation; Methodology; Resources; Supervision; Visualization; Writing—review & editing.

Reviewer information

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