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Long-term surgical outcomes of congenital supravalvular aortic stenosis: a systematic review, meta-analysis and microsimulation study

Frederike Meccanici[a,†], Maximiliaan L. Notenboom [b,†], Jade Meijssen[a,‡], Vernon Smit[a,‡], Pieter C. van de Woestijne [b], Annemien E. van den Bosch[a], Willem A. Helbing [c], Ad J.J.C. Bogers [b], Johanna J.M. Takkenberg [b] and Jolien W. Roos-Hesselink [a,*]

[a] Department of Cardiology, Erasmus University Medical Centre, Rotterdam, Netherlands
[b] Department of Cardiothoracic Surgery, Erasmus University Medical Centre Rotterdam, Netherlands
[c] Department of Paediatrics, Division of Paediatric Cardiology, Erasmus University Medical Centre, Rotterdam, Netherlands

* Corresponding author. Department of Cardiology, Erasmus MC, Room RG-435, PO Box 2040, 3000 CA Rotterdam, Netherlands. Tel: +31-10-7032432; e-mail: j.roos@erasmusmc.nl (J.W. Roos-Hesselink).

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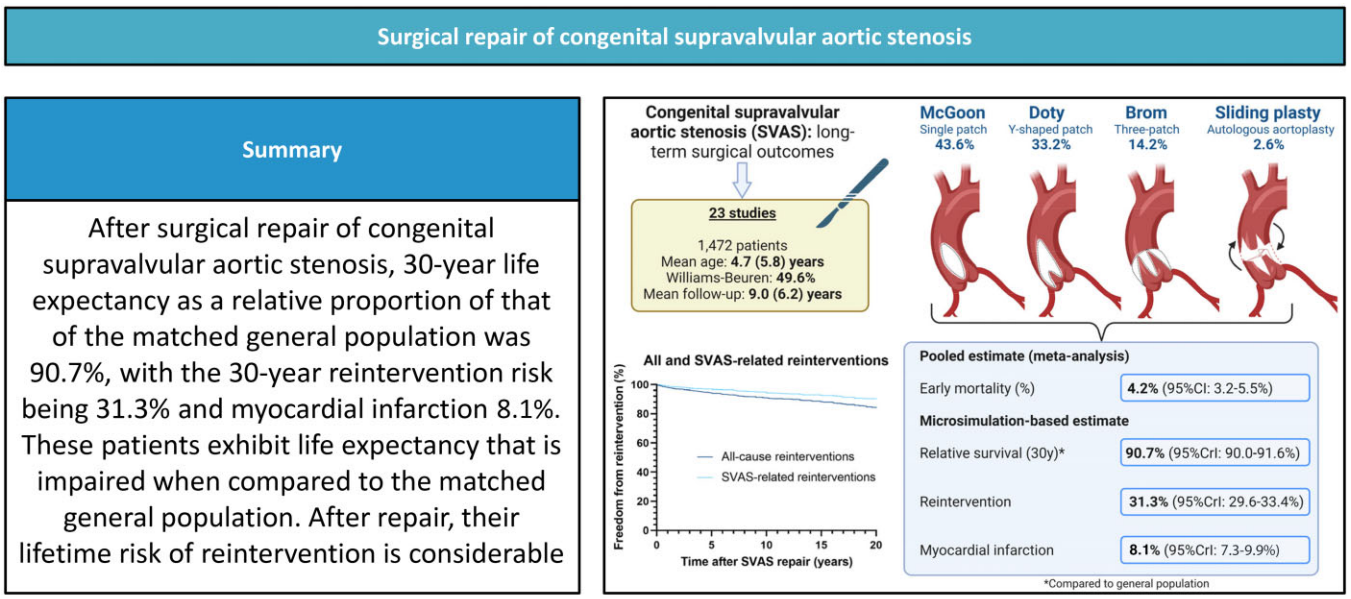

Legend: Summary of microsimulation-based outcomes after congenital supravalvular aortic stenosis repair using all techniques.

Abstract

OBJECTIVES: Congenital supravalvular aortic stenosis (SVAS) is a rare form of congenital outflow tract obstruction and long-term outcomes are scarcely reported. This study aims to provide an overview of outcomes after surgical repair for congenital SVAS.

METHODS: A systematic review of published literature was conducted, including observational studies reporting long-term clinical outcome (>2 years) after SVAS repair in children or adults considering >20 patients. Early risks, late event rates and time-to-event data were

† These authors contributed equally to this work (first authorship).
‡ These authors contributed equally to this work (second authorship).

pooled and entered into a microsimulation model to estimate 30-year outcomes. Life expectancy was compared to the age-, sex- and origin-matched general population.

RESULTS: Twenty-three publications were included, encompassing a total of 1472 patients (13 125 patient-years; pooled mean follow-up: 9.0 (6.2) years; median follow-up: 6.3 years). Pooled mean age at surgical repair was 4.7 (5.8) years and the most commonly used surgical technique was the single-patch repair (43.6%). Pooled early mortality was 4.2% (95% confidence interval: 3.2–5.5%) and late mortality was 0.61% (95% CI: 0.45–0.83) per patient-year. Based on microsimulation, over a 30-year time horizon, it was estimated that an average patient with SVAS repair (mean age: 4.7 years) had an observed life expectancy that was 90.7% (95% credible interval: 90.0–91.6%) of expected life expectancy in the matched general population. The microsimulation-based 30-year risk of myocardial infarction was 8.1% (95% credible interval: 7.3–9.9%) and reintervention 31.3% (95% credible interval: 29.6–33.4%), of which 27.2% (95% credible interval: 25.8–29.1) due to repair dysfunction.

CONCLUSIONS: After surgical repair for SVAS, 30-year survival is lower than the matched-general-population survival and the lifetime risk of reintervention is considerable. Therefore, lifelong monitoring of the cardiovascular system and in particular residual stenosis and coronary obstruction is recommended.

Keywords: Congenital heart defects • Supravalvular aortic stenosis • Congenital cardiac surgery • Systematic review • Microsimulation • Individual patient-data meta-analysis

ABBREVIATIONS

LVOT	Left ventricular outflow
PSA	Probabilistic sensitivity analysis
SD	Standard deviation
STJ	Sinotubular junction
SVAS	Supravalvular aortic stenosis

INTRODUCTION

Congenital supravalvular aortic stenosis (SVAS) is a rare, congenital form of left ventricular outflow (LVOT) tract obstruction, accounting for ∼14% of all paediatric aortic stenosis [1]. SVAS can appear as a discrete narrowing typically located at the sinotubular junction (STJ) or as a diffuse obstruction of the whole ascending aorta and arch branches [2]. The vascular abnormalities observed in congenital SVAS are considered elastin arteriopathy [3], due to a deletion of the elastin gene located on chromosome 7q11.23 [4]. While SVAS can occur spontaneously, in most cases it is associated with genetic disorders such as Williams–Beuren syndrome [5]. Multiple concomitant cardiovascular anomalies are often present, ranging from pulmonary (arterial) stenosis associated with Williams–Beuren syndrome [5], to a wide spectrum of left-sided obstructions, mostly seen in Shone's complex [6].

The clinical presentation of SVAS patients can vary widely depending on the severity and location of the narrowing of the aorta. In mild cases, patients may not exhibit any symptoms, and the condition may only be detected incidentally during a routine physical exam or imaging study. However, in more severe cases, the natural course of SVAS is progressive [7] and surgical treatment might be advised in case of haemodynamically significant stenosis [8].

Different surgical alternatives have been applied over the years, with the 3 most commonly performed procedures being: the McGoon repair (single diamond-shaped patch) since 1956 [9], the Doty repair (pantaloons-shaped patch) since 1977 [10] and the Brom repair (three-patch repair) since 1978 [11]. Additionally, modifications have been proposed, including a technique that involves an interdigitating aortoplasty and avoids the need for patch material, also called a Myers sliding aortoplasty [12]. The transection used during a sliding aortoplasty additionally optimizes the visibility of local endovascular stenosis.

While short-term outcomes have been reported in various studies small in sample size, there is a paucity of data on the long-term outcomes of surgical repair for SVAS and it remains unclear whether 1 technique is superior. Outcomes are scattered across numerous reports and these are also often small in sample size given the infrequent occurrence of SVAS [13].

This systematic review and meta-analysis aim to gather all published evidence on surgical repair for congenital SVAS and employ microsimulation to investigate long-term mean life expectancy compared to the general population, event-free life expectancy and 30-year risks of reintervention and other events after surgical SVAS repair.

MATERIALS AND METHODS

Ethical statement and registration

The protocol for this systematic review and meta-analysis was registered in the PROSPERO registry (CRD42021245185) and approved by the local medical ethics committee of the Erasmus University Medical Centre (MEC-2021-0520). This study was conducted in accordance with the updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [14] (Supplementary Material 1.1).

Search strategy and study selection

On 12 April 2022, MEDLINE, Embase, Web of Science, Cochrane Library and Google Scholar were searched by a biomedical information specialist employing keywords related to surgical correction of congenital SVAS in children and/or adults. The final search string is listed in Supplementary Material 1.2. Titles and abstracts were independently screened by 2 reviewers (Vernon Smit, Jade Meijssen) and in case of disagreement a third reviewer (Frederike Meccanici) was consulted. Inclusion criteria were observational studies reporting on surgical correction of congenital SVAS in paediatric or adult patients considering at least 20 consecutive patients for the quantitative analysis and, in addition, studies with 10–19 patients for the qualitative analysis. Studies needed to provide long-term outcomes after surgery, defined as

a minimum of 2 years after surgery. If a publication was not available, it was obtained by either applying for an interlibrary loan procedure established between university libraries or reaching out to the corresponding author. In case over overlapping study populations, the study encompassing the greatest number of follow-up patient-years for each individual outcome was included.

Data extraction and definitions

Microsoft Office Excel 2016 (Microsoft Corp., Redmond, WA, USA) was used for data extraction. Two reviewers (Vernon Smit, Jade Meijssen) independently extracted study, preoperative and surgical characteristics. All outcome data were independently extracted by 2 reviewers (Frederike Meccanici, Maximiliaan L. Notenboom). The extracted variables of each included study were verified by 2 other, independent reviewers (Maximiliaan L. Notenboom, Frederike Meccanici). In case of disagreement on any reported value, an agreement was reached through consensus. For the quantitative analysis, all recorded study characteristics, baseline patient characteristics, operative details and outcome measures are enclosed in Supplementary Material 1.3. Also, risk factors for early and late mortality and reintervention based on multivariable regression analyses of the included studies were collected. For studies including 10–19 patients, the following variables were collected: age at surgery, country, surgical technique(s), inclusion period, follow-up time, early mortality and reintervention and late mortality and reintervention.

Functional class before and after surgical intervention was reported according to the New York Heart Association classification for adults or the modified Ross classification for heart failure in children [15]. Mortality and morbidity were documented according to the 2008 guidelines by Akins [16]. Early outcome events were defined as events occurring within the first 30 days after surgery. Late outcome events were defined as occurring after the first 30 days after surgery. If the total number of patient-years was not reported, it was calculated by multiplying the mean follow-up duration with the number of patients.

After correction, repair dysfunction was defined as a residual (early) or reoccurrence (late) of a mean gradient of ≥40 mmHg. Reinterventions for repair dysfunction and other causes (e.g. endocarditis) were documented separately as a subgroup of total reinterventions. SVAS-related reintervention was defined as reintervention on the aortic valve, aortic root or ascending aorta, or coronary ostia reimplantation. Non-SVAS-related cardiac reintervention was defined as reintervention on the aortic arch or descending aorta and other cardiac interventions such as pulmonary artery reconstruction.

Quality assessment

Quality assessment of the studies included in the quantitative analysis was performed independently by 2 reviewers (Vernon Smit, Jade Meijssen) according to the 'Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies' [17].

Statistical analyses

All statistical software used is described in Supplementary Material 1.4. Continuous variables are presented as mean and standard deviation (SD). Categorical variables are presented as counts and percentages. Linearized occurrence rates (assuming constant hazard rates over time) of events are presented as percentages per year and were calculated by dividing the number of reported events per study by the total number of patient-years of follow-up for that study. Baseline and surgical characteristics were pooled through sample size weighting and the range of the values among included studies was reported. Conversely, inverse variance weighting was carried out for pooling event risks (early), according to the number of patients, and event rates (late), according to the number of patient-years of follow-up. All outcomes were pooled on a logarithmic scale, as the Shapiro-Wilk test and density plots revealed a significantly skewed distribution among the majority of the outcomes. The estimation of between-study variance was performed according to the DerSimonian and Laird [18] method in a random-effects model. In case no events in a particular outcome occurred in a study, it was assumed that 0.5 patients in this cohort experienced the event for pooling purposes (continuity correction). *P*-values <0.05 were considered statistically significant.

The presence of 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.

Kaplan–Meier meta-analysis. Estimates of individual patient time-to-event data, derived from published Kaplan–Meier curves, were extracted and combined using the method described by Guyot *et al.* [19]. First, all published Kaplan–Meier curves for the outcomes of interest (survival, all-cause reinterventions, SVAS-related reinterventions) were digitized. Thereafter, all estimated time-to-event data of all individual patients were digitally extracted from this curve. The assumption of a linear censorship rate was made between each time point at which the remaining number of patients still at risk were specified [19]. When no Kaplan–Meier data were available for a time-to-event outcome, the individual patient time-to-event data were manually reconstructed from the manuscript text in case authors reported time points at which the events occurred or if no events occurred at all [19]. In case no numbers at risk were reported throughout the study, the reconstruction was attempted by assuming a maximum follow-up of the reported mean follow-up plus 2 SDs, also under the same assumption of a constant rate of censorship. Lastly, the time-to-event data of each individual study were combined for each time-to-event outcome, to generate pooled time-to-event data and construct Kaplan–Meier curves. A subgroup analysis in time-to-event outcomes was performed for patients with Williams–Beuren Syndrome versus those without Williams–Beuren Syndrome.

Heterogeneity. To investigate the proportion of total heterogeneity for each outcome that was ascribable to between-study heterogeneity, the Cochran-*Q* statistic and I^2 statistic were used. Also, univariable random effects meta-regression was performed to investigate potential causes of heterogeneity in the main outcome measures: early mortality, late mortality and reintervention. The effect of patient and surgical characteristics listed in Table 1 as well as the median year of surgery on the outcomes of interest was investigated.

Table 1: Summarized patient characteristics and operative details

Variables	Pooled estimate	Range	Studies (*n*)
Patient characteristics			
Age (years), mean (SD)	4.68 (5.84)	2.2–14.3	23
Male (%)	62.1	44.9–72.7	22
Weight (kg), mean (SD)	20.7 (17.1)	11.5–36.9	14
Discrete type SVAS (%)	71.7	14.3–100	20
Diffuse type SVAS (%)	28.0	0.0–85.7	20
Williams–Beuren syndrome (%)	49.6	13.9–100	22
Sporadic SVAS (%)	30.9	0.0–58.8	7
NYHA class >I (%)	62.3	9.9–89.1	5
Symptomatic (%)	44.0	23.0–91.0	5
Associated cardiovascular anomalies			
Concomitant anomalies (%)[a]	80.4	13.0–100	19
Branch and/or peripheral PA stenosis (%)	20.1	0.0–65.0	21
AV stenosis (%)	17.0	0.0–34.7	15
Aortic anomalies (%)	13.0	0.0–100	16
Aortic coarctation (%)	6.38	0.0–26.5	18
Aortic arch abnormality (%)	2.33	0.0–10.7	16
BAV (%)	11.1	0.0–38.9	18
AV regurgitation (%)	6.44	0.0–30.6	15
Coronary anomaly (%)	10.8	0.0–28.0	17
Coronary stenosis (%)	6.89	0.0–36.0	19
SAS (%)	7.99	0.0–30.6	16
(Sub)pulmonary valve stenosis (%)	3.84	0.0–22.5	18
VSD (%)	2.65	0.0–10.9	17
Previous cardiac interventions			
Previous interventions (%)[a]	24.3	3.6–47.5	10
Aortic surgery (%)	6.98	0.0–16.0	9
Coarctectomy (%)	5.95	0.0–16.0	11
Aortic valvuloplasty/valve repair (%)	3.12	0.0–11.1	9
SAS resection (%)	1.19	0.0–8.3	9
SVAS resection (%)	0.74	0.0–8.3	9
VSD closure (%)	0.74	0.0–4.0	9
Other/unknown	9.59	0.0–25.5	11
Operative characteristics SVAS repair			
Type of SVAS repair			
McGoon repair/single-patch repair (%)	46.3	0.0–100	23
Doty repair/Y-shaped/pantaloons shaped patch (%)	33.2	0.0–100	23
Brom repair/three-patch repair (%)	14.2	0.0–100	23
Myers sliding aortoplasty (%)	2.63	0.0–52.0	23
Other/unknown (%)	3.66	0.0–30.6	23
Concomitant procedures			
Concomitant procedures excluding SVAS/SAS/AV (%)[a]	31.4	0.0–107.9	22
Pulmonary and other procedures (%)	24.5	3.85–73.0	22
Aortic surgery (%)	3.65	0.0–20.6	22
Other valve repair/replacement (%)	2.60	0.0–16.7	22
AV surgery (%)	10.3	0.0–38.9	22
SAS resection (%)	5.61	0.0–30.6	22

Pooled percentages are depicted for categorical variables and pooled mean/median with standard deviation in parentheses for continuous variables. The range of the mean/median values or percentages in the reporting studies is presented.

[a]The number of concomitant anomalies and interventions are reported; therefore, the percentage can reach higher than 100% as multiple concomitant anomalies of cardiac interventions could be reported per patient.

AV: aortic valve; BAV: bicuspid aortic valve; NYHA: New York Heart Association; PA: pulmonary artery; SAS: subvalvular aortic stenosis; SD: standard deviation; SVAS: supravalvular aortic stenosis; VSD: ventricular septal defect.

Microsimulation. Microsimulation models provide a unique opportunity to gain insights into age-specific life expectancy and lifetime risks of disease-related events. Its methodology and structure have been previously described [20–23]. To estimate life expectancy and risks of SVAS-related morbidity after congenital SVAS repair, a microsimulation model based on the pooled early and late outcome estimates of this meta-analysis was employed (Supplementary Material 1.6). As pooled follow-up duration was too short to draw inferences about lifetime risks after SVAS repair, occurrence rates of valve-related events were extrapolated slightly beyond the extent of the observation period of this meta-analysis, up to a period of 30 years.

Occurrence of reintervention was modelled according to the flexible parametric survival model that best fitted the pooled Kaplan–Meier data of reintervention, which was the Gompertz distribution. Unfortunately, no time-to-event data were available for other SVAS-related events (bleeding, thrombo-embolism, cerebrovascular accident, endocarditis). Hence, constant hazards for these events were assumed in our simulation.

All-cause mortality can be divided into death directly due to SVAS-related causes and deaths not directly due to SVAS-related causes, the latter of which consists of both matched-general-population mortality in the general population (also known as background mortality) and excess mortality that does not directly result from SVAS-related events, but is only observed after SVAS repair [20]. Matched-general-population mortality was obtained by weighting lifetable estimates from countries of included studies. Lifetables were retrieved from the Human Mortality Database (Supplementary Material 1.7). Median year of intervention, proportion of men and age in studies from each individual country were calculated. These estimates per country were weighted by using each country's proportions of the total meta-analysis population. The mortality probabilities for men and women of each age were calculated (Supplementary Material, Datasheet 1) and these were used during the simulation. A detailed description of matched-general-population mortality estimation and the estimation of the hazard ratio for excess mortality are described in Supplementary Material 1.7.

Probabilistic sensitivity analysis (PSA) was performed to take the uncertainty in input parameters of the microsimulation into account and to include the implications of this uncertainty into the modelled outcomes. In the PSA, the model considered a sample of 1000 patients per set and ran for 500 different sets of randomly drawn input parameters. Details of the PSA are elucidated in Supplementary Material 1.7.

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 and SD of age and proportion of males in studies included in the pooled Kaplan–Meier for late mortality. The Kaplan–Meier curve for all-cause mortality obtained from this microsimulation was plotted against the pooled Kaplan–Meier survival curve derived from the meta-analysis in a calibration plot (both excluding early mortality).

RESULTS

Systematic review

Figure 1 shows the flowchart of study selection. Finally, 23 studies were included in the quantitative analysis of this systematic

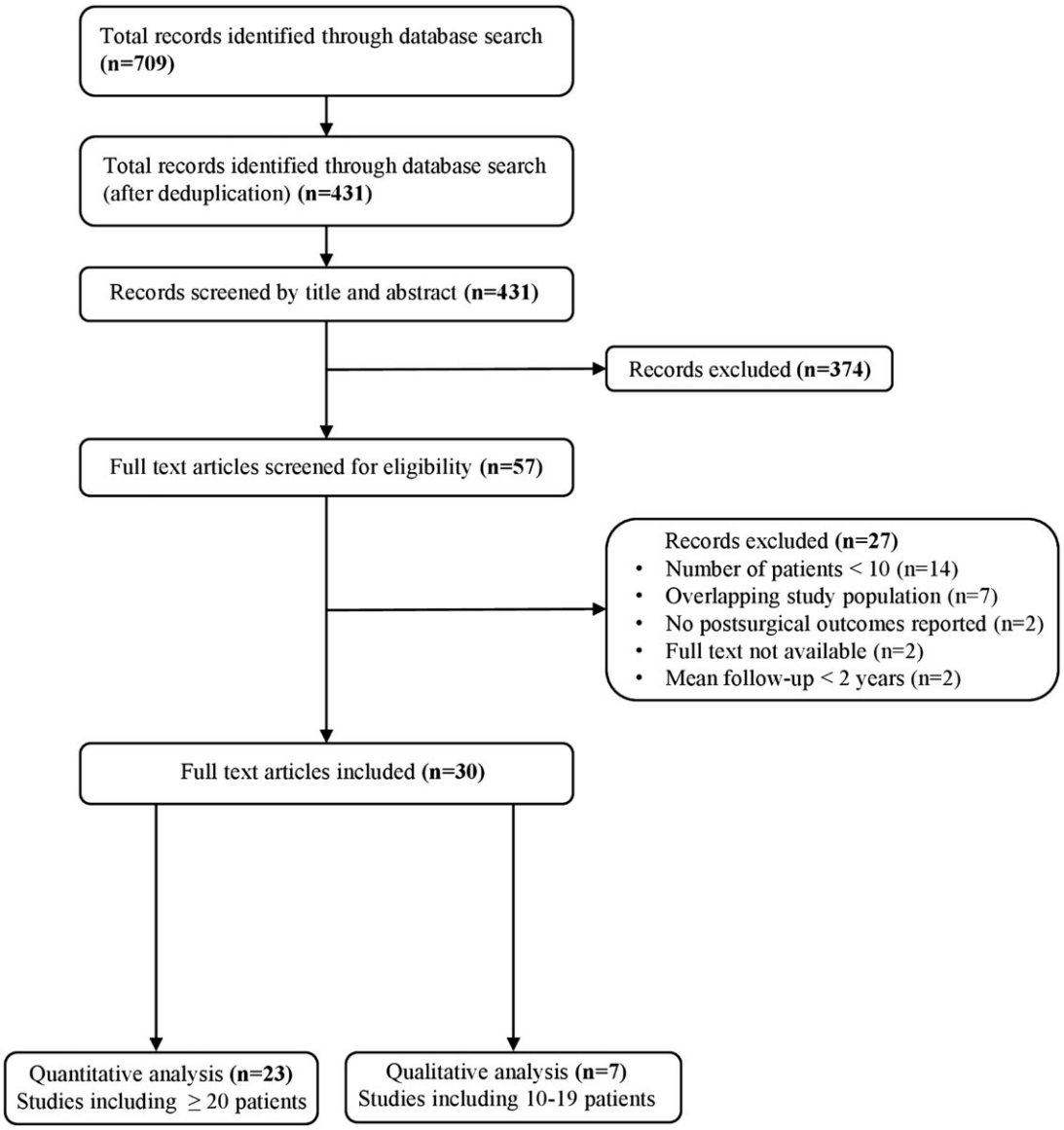

Figure 1: Flowchart of study selection.

review with a total of 1472 patients (62% male), all of whom were retrospective cohort studies [24–46]. The number of included patients ranged from 21 [24] to 301 [23] patients with a pooled mean follow-up time of 9.0 [SD: 6.2 years (median: 6.3 years, range: 2.5–19.8 years)], encompassing a total of 13 125 patient-years. Study characteristics and results of quality assessment are shown in Supplementary Materials 2 and 3, respectively. For the studies including 10–19 patients ($n = 7$), the study characteristics and outcomes are described in Supplementary Material 4.

Meta-analysis

Summarized patient and operative characteristics are shown in Table 1. Overall, the most commonly used surgical technique was the single-patch technique with a pooled percentage of 43.6 (range: 0.0–100.0%) among included studies. A total of ∼5% of patients underwent postsurgical correction of supravalvular stenosis after earlier LVOT and/or VSD surgery. Early and late pooled outcomes are depicted in Table 2. The pooled Kaplan–Meier curves for all-cause mortality, all-cause reinterventions and SVAS-related reinterventions, are shown in Figure 2. The pooled Kaplan–Meier curve for all-cause mortality and freedom from left-sided reintervention, stratified for patients with Williams–Beuren syndrome versus without Williams–Beuren syndrome are provided in Supplementary Material 5. With regard to haemodynamics of SVAS; the pooled mean peak gradients were 82.0 (SD: 30.4) mmHg preoperatively, 17.2 (SD: 14.5) mmHg in the early postoperative period and 18.5 (SD: 7.4) mmHg in the late follow-up, reported in 15 studies ($n = 901$).

Microsimulation

Based on the microsimulation model, over a 30-year time horizon, it was estimated that an average patient with congenital SVAS repair (mean age: 4.7 years) had an observed life expectancy that was 90.7% (95% credible interval: 90.0–91.6%) of expected life expectancy in the matched general population. The

Table 2: Pooled early event risks and late event rates after surgical repair of congenital supravalvular aortic stenosis

Variables	Pooled estimate (95% CI)	I^2	Q-test	Reporting studies (*n*)
Pooled early event risks (%)				
Mortality (%)	4.18 (3.19–5.47)	0	0.817	23
Reintervention (%)	3.25 (2.29–4.61)	0	0.762	22
SVAS related	1.26 (0.73–2.19)	0	0.998	22
Non-SVAS related, cardiac	2.56 (1.70–3.84)	0	0.841	20
Re-exploration for bleeding	1.40 (0.82–2.37)	0	0.991	20
Obstruction LVOT (peak gradient ≥40 mmHg) (%)	16.70 (12.50–21.90)	0	0.502	7
Endocarditis (%)	1.36 (0.67–2.77)	0	1	15
Thrombo-embolism (%)	1.77 (0.80–3.91)	0	0.98	10
Bleeding (%)	2.17 (1.23–3.83)	0	0.673	10
CVA (stroke + TIA) (%)	2.14 (0.68–6.77)	53	0.03	9
Stroke (%)	1.52 (0.83–2.81)	0	0.552	15
TIA (%)	2.50 (1.14–5.48)	0	0.568	9
MI (%)	1.39 (0.84–2.29)	0	0.999	18
Pacemaker implantation (%)	1.64 (0.62–4.32)	0	0.927	7
Pooled linearized occurrence rates (%/PTY)				
Late mortality (%)	0.61 (0.45–0.83)	21.8	0.171	23
Cardiac death	0.47 (0.35–0.61)	0	0.72	23
SVAS related	0.38 (0.27–0.53)	0	0.668	23
SUD	0.36 (0.24–0.55)	0	0.996	21
Late reintervention (%)	2.10 (1.54–2.86)	77.6	<0.001	21
SVAS related	1.38 (1.00–1.90)	64.9	<0.001	22
Aortic valve	0.88 (90.60–1.27)	54.5	0.001	22
Non-operated-SVAS-related cardiac	0.80 (0.51–1.24)	68.4	<0.001	21
Late endocarditis (%)	0.18 (0.09–0.36)	0	0.658	14
Late thrombo-embolism (%)	0.16 (0.04–0.55)	28.8	0.23	5
Late bleeding (%)	0.23 (0.08–0.73)	0	0.799	6
Late CVA (stroke + TIA) (%)	0.31 (0.10–0.97)	0	0.758	6
Late stroke (%)	0.19 (0.09–0.04)	0	0.952	13
Late TIA (%)	0.31 (0.10–0.97)	0	0.758	6
Late MI (%)	0.24 (0.10–0.55)	0	0.975	10
Pooled proportions (%)				
NYHA class >I (%)	12.30 (4.57–20.10)	77.8	<0.001	6
Aortic regurgitation (≥moderate) (%)	4.76 (2.67–6.84)	34.9	0.089	15

Pooled predictions are depicted including 95% CI. Heterogeneity between studies is shown with the I^2 and the Q-test.
CI: confidence interval; CVA: cerebrovascular accident; LVOT: left ventricular outflow tract; MI: myocardial infarction; NYHA: New York Heart Association; PTY: Patient-years; SUD: Sudden, unexplained death; SVAS: supravalvular aortic stenosis; TIA: transient ischaemic attack.

estimated 30-year risks of SVAS-related complications are presented in Figure 3. The microsimulation model calibration with the pooled mortality and reinterventions resulting from the meta-analysis are available in Supplementary Material 6. The hazard ratio for excess mortality relative to the matched-general-population mortality was 0.85 (Supplementary Material 7).

Risk factors

In 6/23 included studies, a multivariable risk factor analysis was performed for early or late mortality and/or reintervention [24, 27, 28, 30, 33, 45]. Independent risk factors for early mortality were reported: age <1 year [24] and the type of operation and type of stenosis (diffuse) [45]. For late mortality, age <1 year [24], male sex [24], pulmonary artery stenosis [24] and aortic valve stenosis [24, 28], residual gradient >40 mmHg [28], diffuse stenosis [45] were reported as independent risk factors. For early reintervention, the single diamond-shaped patch was found associated in Stamm *et al.* [2]. For late reintervention factors independently associated were: enrolment year (2006–2015) [24], brachiocephalic vessel stenosis [24] and LVOT obstruction [24, 27], preoperative aortic valve disease [28], younger age at surgery [33] and type of stenosis (diffuse) [45]. Furthermore, in Brown *et al.* [27], no independent risk factors for late mortality were identified and in Hickey *et al.* [30], no significant independent risk factors for mortality and reoperation were identified.

Sensitivity analysis

The sensitivity analysis did not reveal possible publication bias in the pooled outcome estimates for early and late mortality and reintervention. When excluding the smallest quartile of included studies based on sample size, the pooled outcome estimates were comparable with the analysis including all studies (Supplementary Material 8).

Heterogeneity

Individual estimates of the univariable random-effects meta-regression for early mortality and reintervention and late mortality and reintervention are shown in Supplementary Material 9. A more recent year of publication and median surgical year were

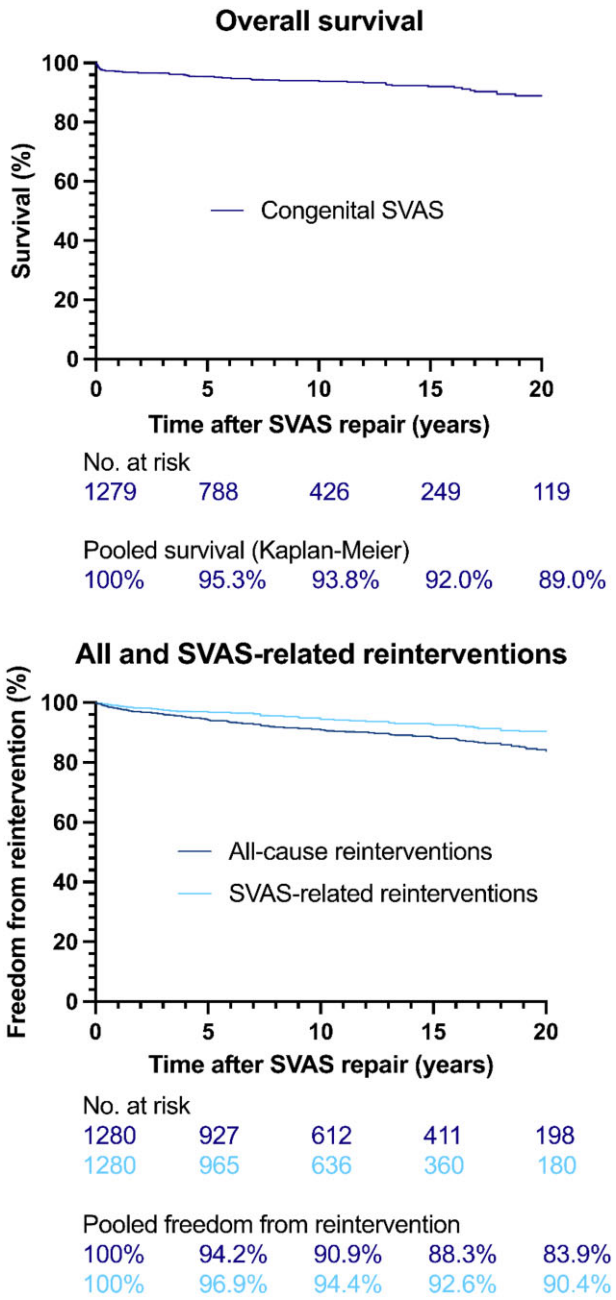

Figure 2: Pooled Kaplan–Meier estimates for survival (**A**) and all-cause and SVAS-related reinterventions (**B**). SVAS: supravalvular aortic stenosis.

significantly associated with lower early mortality risks [beta estimate: -0.03 (95% confidence interval: -0.06 to -0.01), $P = 0.004$ and -0.02 (-0.03 to -0.01), $P < 0.001$].

DISCUSSION

To the best of our knowledge, this is the first study to provide a comprehensive overview of all published literature on outcomes after surgical repair for congenital SVAS. Congenital SVAS is a rare and complex disease with multiple associated cardiac anomalies and syndromes. Combining data of 23 publications encompassing a total of 13 125 patient-years, we found that the pooled early mortality was 4.2% and late mortality 0.6% per patient-year. In the first 30 postoperative years, patient survival was 90.7% of survival expected in an age-matched, sex-matched and origin-matched general population. Lastly, it was estimated that around one-third of patients required reintervention and myocardial infarction occurred in ∼8.1% during the first 30 postoperative years, posing a considerable risk.

Mortality and reintervention

The pooled early mortality in this meta-analysis was 4.2% (95% confidence interval: 3.2–5.5) and, during follow-up, a late mortality rate of 0.6%/year (0.5–0.8%/year) was observed. Of note, the risk of sudden, unexplained death (or unknown death) during follow-up was particularly high at 0.4%/year (0.24–0.6%/year), comprising a substantial proportion of total observed mortality. In Williams–Beuren syndrome, of which around 69% is diagnosed with SVAS [47], the risk of sudden cardiac death was 0.1%/year compared with 0.001%/year in the age-matched general population [48]. Given that patients with Williams–Beuren syndrome who experienced sudden death likely exhibited myocardial ischaemia caused by coronary artery stenosis and severe biventricular outflow tract obstruction [49], it is probable that congenital SVAS patients also face an increased risk of sudden death.

Life expectancy in the first 30 postoperative years after congenital SVAS repair was impaired compared to the age-matched, sex-matched and origin-matched general population, with a relative life expectancy of 90.7%. After SVAS repair, there was a substantial reoccurrence risk of some degree of recurrent SVAS, which poses patients at risk for multiple reinterventions, ventricular failure and coronary flow obstruction. Additionally, perioperative myocardial ischaemia was not uncommon, posing patients at risk for late myocardial dysfunction. These cumulative effects may pose patients at a greater risk of death compared to the general population, even after hospital discharge. It is worth noting that the risk of coronary obstruction appears to be independent of SVAS gradients, and catheter interventions carry their own set of risks in this particular group of patients [50]. Therefore, screening for coronary obstruction in the perioperative period and during follow-up after SVAS repair with the use of non-invasive methods such as cardiac tomography or magnetic resonance imaging, is recommended. In 2018, Roemers *et al.* [43] also concluded that after SVAS repair, survival was impaired compared to the general Dutch population. Excess mortality in our study was low with a hazard ratio of 0.85 relative to the matched-general-population mortality. This, coupled with very low mortality in the general population at this age (Supplementary Material, Datasheet 1), makes it reasonable to believe that there is no excess mortality other than SVAS-related mortality and matched-general-population mortality in this population.

Regarding reinterventions, the pooled rate was estimated at 2.1%/year (1.5–2.9%/year), comparable with pooled reintervention rates observed after paediatric SAS repair [2.0%/year (0.6–6.4%/year)] [51]. The burden of reintervention during follow-up is substantial: based on the microsimulation, around one-third of all SVAS patients would require reintervention during the first 30 postoperative years. The majority of reinterventions was due to repair dysfunction, highlighting the chronic and progressive nature of SVAS. While we observed that reinterventions were not associated with mortality during follow-up, such procedures could still result in significant morbidity and have an impact on

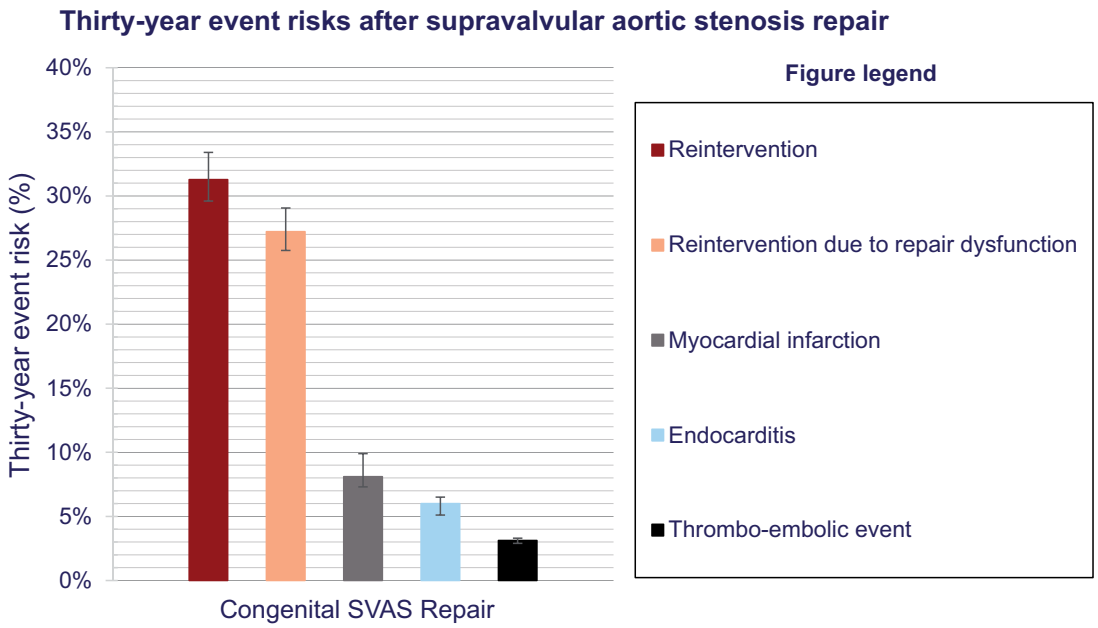

Figure 3: Microsimulation-based event risks in the first 30 postoperative years after congenital SVAS repair. Values represent the 30-year events risks (point estimate) in percentages and the error bars show the upper and lower boundaries of the 95% credible interval derived from the probabilistic sensitivity analysis. SVAS: supravalvular aortic stenosis.

patient's quality of life. SVAS remains a complex heterogeneous disease, requiring careful preoperative planning and consideration of specific patient-related factors.

According to the pooled Kaplan–Meier curves (Supplementary Material 4), patients with Williams–Beuren syndrome appeared to have different temporal patterns of mortality and left-sided reinterventions compared to those without Williams–Beuren syndrome, although absolute differences were minor. In patients without Williams–Beuren syndrome, mortality and reintervention hazards seemed more pronounced in earlier postoperative years. Unfortunately, little data is available on the comparison between patients with or without Williams–Beuren syndrome in current literature.

Surgical techniques

Over the years, several surgical techniques and modifications have been adopted. McGoon *et al.* [9] first introduced a single-patch repair, extending into the non-coronary sinus to enlarge the STJ and relief obstruction. Later, Doty *et al.* [10] developed a two-patch, pantaloons-shaped patch technique also involving the right coronary sinus. Brom aortoplasty, often referred to as three-patch repair, followed in 1978 and resulted in the most geometrical configuration of the proximal aorta, allowing for optimal haemodynamics [11]. All 3 techniques involve use of patch material, which has fuelled the development of a sliding, 'interdigitating' aortoplasty in 1993 [12], avoiding the need for patches and enabling growth potential in young children. The surgical technique should be aimed at repair of the obstruction while restoring root geometry and anatomy. An ongoing debate is taking place on the preferred surgical technique.

Large studies comparing single, pantaloons-shaped and three-patch repair found comparable mortality and reintervention rates [24, 52]. Stamm *et al.* [45] concluded that pantaloons-shaped and three-patch repairs exhibited better outcomes compared to single-patch repairs in terms of mortality and reintervention, although follow-up was substantially longer for single-patch repairs. Similarly, Kaushal and colleagues found lower reintervention rates after three-patch repair, again with short follow-up duration [35]. Contrarily, both Brown *et al.* [27] and Deo *et al.* [13] concluded that the single-patch repair is a reproducible, effective technique for SVAS correction. Other authors suggest that a pantaloons-shaped or three-patch repair allows for greater STJ diameters and has lower hazards of reintervention over time compared to a single-patch repair [32]. Nonetheless, patient characteristics varied significantly between techniques. Ibarra and colleagues compared one-patch with pantaloons-shaped repairs and found that the latter technique was more often adopted in younger children and had a greater proportion of discrete stenosis and Williams–Beuren syndrome [32]. Greater STJ diameters and lower SVAS-related reintervention rates were observed after a pantaloons-shaped repair [32]. Metton *et al.* [40] and Fricke *et al.* [29] both reported no deaths and no reoperations after three-patch repair, albeit with a mean follow-up of 5 years. Based on our systematic review and meta-analysis, we are of the conclusions that the optimal surgical technique for an individual patient should be tailored to that individual, based on the unique anatomy, associated lesions and patient-specific (clinical) characteristics. Surgeon preference will likely play a role. The three-patch repair was introduced relatively late (1978), which has led follow-up duration to be longer for single and pantaloons-shaped repair cohorts. For these reasons, direct comparison of techniques may lead to confounding by indication and was not performed in this meta-analysis.

It can be concluded that there currently is no consensus on a preferred technique and the actual technique in an individual seems to be determined by SVAS anatomy and centre and surgeon preference. An additional manual search was performed on 30 September 2023. Two recent studies [53, 54] that were not included in this meta-analysis have shown promising results with

modified techniques, which require meticulous long-term follow-up to determine their position in the surgical armamentarium for SVAS.

Risk factors

Several independent risk factors for mortality and reintervention were identified in the included studies. Age <1 year at the time of surgery was associated with mortality [24] and reintervention [33], probably reflecting the severe disease stage of these patients. Furthermore, concomitant aortic valve disease seems to be associated with late mortality [24, 28] and reintervention [28]. An explanation for this increased risk could be valve-related morbidity and interventions. Moreover, aortic valve stenosis as additional source of left ventricle outflow tract obstruction can expose the left ventricle to high pressures, resulting in ventricular decompensation, heart failure and severe arrhythmias. Lastly, the type of stenosis and extent of obstruction also seems to affect prognosis [45]. As mentioned previously, diffuse SVAS might require more elaborate surgical techniques and it represents a severe vascular arteriopathy affecting multiple vessels. Combining all the available cohorts in a registry with pre-specified variables and considerable follow-up duration, would help identifying risk factors and provide more valuable estimates for mortality and morbidity.

Insights into these risk factors may be used to guide decision-making and inform clinicians and (parents of) patients with congenital SVAS regarding risk factors for specific outcomes. Reintervention was the most common event related to the SVAS. Typically, the younger patient (infant) with aortic valve disease, concomitant LVOT obstruction and diffuse stenosis of the supravalvular aorta with a distally extending stenosis is at highest risk for reintervention after surgical repair according to these results.

Limitations

The present study is a systematic review and meta-analysis of observational studies, all retrospective in design. Therefore, it is important to consider the inherent limitations of meta-analysis and the combining of data from retrospective observational studies [55]. Publication bias is possibly present, and this might have influenced our results. The presence of publication bias was not explored by 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 itself [56]. However, the quartile of smallest studies, by sample size, was temporarily excluded as an alternative to investigate publication bias. A comparison between surgical techniques was not feasible, due to confounding by indication, different follow-up lengths and surgeon's preferences. Furthermore, as the included studies were of small study size and the number of events was low, the risk factor analyses in these studies should be interpreted with caution due to limited statistical power. Additionally, no age-specific estimates could be generated in the microsimulation due to a paucity of age-specific data in the literature. Also, no competing risk analyses were performed in the meta-analysis, which may lead to an overestimation of time-to-event outcomes other than all-cause mortality. Contrarily, the microsimulation-based estimates—e.g. for reintervention or myocardial infarction—do account for the competing risk of any death. Lastly, this review focuses on congenital SVAS, but a minor proportion of the included patients (~5%) underwent postsurgical SVAS repair—i.e. in the setting of previous aortic valve or SVAS repair with residual stenosis in the supravalvular aorta.

Overall, heterogeneity in the observed early outcomes was acceptable, whereas, for late outcomes, the reintervention rates showed considerable heterogeneity. The only significant source of heterogeneity identified by meta-regression was the surgical year for the outcome early mortality, implying that with an increasing year of surgery in a study, a lower mortality risk was observed. The improved early outcomes observed in recent years are likely due to advancements in diagnosis, optimized surgical timing, improved intensive care and anaesthesia.

This review also underscores that application of microsimulation is not always able to generate patient-specific outcome estimates that may be used in clinical practice. Under the right circumstances, i.e. when enough data regarding clinically relevant subgroups is available, microsimulation may provide tailored outcome estimates for individual patient or subgroups of patients, i.e. age-specific and sex-specific risks of mortality and reintervention over a lifetime. Data used in the current analysis was relatively scarce (23 studies) and did not report on relevant subgroups of sufficient sample size for microsimulation purposes, hampering the provision of patient-specific outcome estimates in this study. Nonetheless, Kaplan–Meier data was reconstructed for patients with Williams-related SVAS and non-Williams-related SVAS. Furthermore, microsimulation provided insights into very long-term outcomes for the average SVAS patient, which may also be useful in clinical practice, but in a less patient-tailored manner.

CONCLUSION

Based on this systematic review and meta-analysis, 30-year life expectancy for patients after surgical repair for congenital SVAS is significantly lower than in the matched general population. Sudden death, myocardial infarction and reintervention are reported during follow-up, underlining the need for lifelong monitoring of the cardiovascular system. Patient-related factors such as younger age, associated aortic valve disease and diffuse type stenosis seemed to have worse prognosis. Congenital SVAS is a highly complex disease, warranting a patient-specific approach in perioperative planning and follow-up. The ideal surgical technique for an individual patient should be based on their unique characteristics and SVAS anatomy and aimed at complete repair of the obstruction while restoring root anatomy. Future studies with longer follow-up duration on the more recently developed surgical techniques, should provide more insights.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

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DATA AVAILABILITY

All data and analytical methods will be made available upon reasonable request.

Author contributions

Frederike Meccanici: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Software; Validation; Visualization; Writing—original draft; Writing—review & editing. **Maximiliaan L. Notenboom:** Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Software; Validation; Visualization; Writing—original draft; Writing—review & editing. **Jade Meijssen:** Data curation; Investigation; Methodology. **Vernon Smit:** Data curation; Formal analysis; Methodology. **Pieter C. van de Woestijne:** Conceptualization; Formal analysis; Investigation; Methodology; Supervision; Validation; Visualization; Writing—review & editing. **Annemien E. van den Bosch:** Conceptualization; Investigation; Methodology; Resources; Supervision; Validation; Visualization; Writing—review & editing. **Willem A. Helbing:** Supervision; Validation; Visualization; Writing—review & editing. **Ad J.J.C. Bogers:** Conceptualization; Investigation; Methodology; Resources; Supervision; Validation; Visualization; Writing—original draft; Writing—review & editing. **Johanna J.M. Takkenberg:** Conceptualization; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Visualization; Writing—review & editing. **Jolien W. Roos-Hesselink:** Conceptualization; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Visualization; Writing—review & editing.

Reviewer information

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