openheart

Clinical course and outcomes of supravalvular aortic stenosis in adults

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► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/openhrt-2025-003355).

To cite: de Keijzer AR, Keuning ZA, Meccanici F, *et al*. Clinical course and outcomes of supravalvular aortic stenosis in adults. *Open Heart* 2025;**12**:e003355. doi:10.1136/openhrt-2025-003355

Received 31 March 2025
Accepted 14 May 2025

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ABSTRACT

Background Supravalvular aortic stenosis (SVAS) is a rare condition with limited data on patients beyond childhood. This study aims to investigate the clinical course and outcomes of SVAS in adults.

Methods All adult (≥18 years) patients with SVAS, prospectively registered in the Dutch Congenital Cor Vitia database between 2001 and 2019, were included. Survival and event-free survival were assessed. Evolution of peak velocity was analysed using linear mixed models. Differences in previous operated state, sex and Williams-Beuren syndrome were explored.

Results 65 patients were included (age: 23 (IQR: 20, 31) years, 31% female, 46% previous SVAS correction, 47% Williams-Beuren syndrome). The peak velocity was 2.3±1.0 m/s at inclusion. Median follow-up time was 13 (IQR: 10, 17) years. Four patients died (one patient after cardiac surgery, two of non-cardiac causes and in one patient the cause of death was unknown) resulting in a 10-year survival of 95% (95% CI 90% to 100%) and event-free survival of 83% (95% CI 74% to 93%). There were no differences in event-free survival between previous operated state (p=0.2), sex (p=0.48) or Williams-Beuren syndrome (p=0.85). 31 cardiovascular events occurred in 15 patients, with the majority being arrhythmias. All SVAS-related interventions (three surgeries in two patients) occurred in unoperated patients (7 (95% CI 2 to 21)/1000 patient years). Although no patient showed fast progression (≥0.3 m/s/year), the peak velocity evolution over time increased faster in females compared with males (first time spline: 0.8 m/s, p=0.017).

Conclusion In adulthood, SVAS patients showed a stable clinical course without rapid progression. While cardiovascular events occurred in this young cohort, they were mostly obsereved in those with additional congenital heart defects, suggesting a more optimistic view for SVAS itself. No significant differences in outcomes were observed in patients with/without Williams-Beuren syndrome. Overall, SVAS tends to follow a more benign course in adulthood compared with childhood, potentially allowing for less intensive follow-up- though follow-up should still be individualised based on associated congenital heart defects and cardiovascular risks.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Supravalvular aortic stenosis (SVAS) is a rare congenital heart disease, known to be progressive during childhood.

WHAT THIS STUDY ADDS

⇒ In adults with SVAS (during a median follow-up duration of 13 years), survival at 10 years was excellent, but cardiovascular events were considerable, primarily occurring in patients with concomitant congenital heart disease. Repeated measurement analyses of peak velocity showed no to mild progression of SVAS in adults, although women showed faster progression compared with men.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Adult patients with SVAS can be informed about the mild progression of the condition, potentially allowing for less frequent follow-up in selected cases. However, follow-up schedules should be tailored to each patient, taking into account SVAS progression but also concomitant congenital heart disease and the risk of cardiovascular events, which were observed in a notable proportion of this relatively young cohort. While there may be some indication of a more aggressive disease course in women, the clinical implications appear limited, given the overall mild trajectory of SVAS in adulthood.

INTRODUCTION

Supravalvular aortic stenosis (SVAS) is a rare congenital heart disease (CHD) involving an obstruction of the left ventricular outflow tract (LVOT), with an estimated incidence of 1:20 000 births.[1 2] SVAS can appear as a discrete obstruction involving the sinotubular junction or as a diffuse stenosis involving the entire ascending aorta and the aortic arch branches.[3] SVAS is considered a systemic arteriopathy and in non-syndromic cases linked to an autosomal dominant (pathogenic) variation in the elastin gene.[4 5] SVAS is commonly associated with Williams-Beuren syndrome, where it occurs alongside other CHDs like pulmonary stenosis (both valvular and peripheral) and aortic coarctation.[6]

The presentation of SVAS varies depending on the location and severity of the stenosis

and the presence of other concomitant anomalies. Most patients are diagnosed during childhood, often presenting with a systolic murmur or symptoms.[4] At a young age, SVAS often progresses, requiring early intervention after diagnosis in more than half of the children.[7 8] In adults, surgery is recommended when the peak velocity reaches ≥40 mm Hg, while earlier intervention is indicated in symptomatic patients.[9] Several surgical techniques are used for SVAS repair:[10] the McGoon repair (single diamond-shaped patch),[11] the Doty repair (pantaloons-shaped patch),[12] the Brom repair (three-patch repair)[13] and a technique that avoids patch material, called Myers sliding aortoplasty.[14] The available literature reports slow progression in adulthood.[15] The question remains how often follow-up is needed for these patients and how many events occur in operated and unoperated adults, especially as the coronary arteries are incorporated in the high-pressure compartment with fear of early coronary artery disease.[16] Sex differences in cardiovascular disease are increasingly recognised with distinct patterns in disease progression and outcomes. In conditions like bicuspid aortic valve and aortic dilatation, sex-specific variations in aortic growth and events have been reported.[17 18] Furthermore, patients with Williams-Beuren are known to have different temporal patterns of mortality and left-sided reinterventions compared with those without.[10] But detailed analyses stratified by operated/unoperated patients, sex and Williams-Beuren syndrome remain limited in adults with SVAS. Therefore, the aim of this study is to investigate the clinical course and outcomes of adult patients with SVAS with an emphasis on differences in previous operated state, sex and Williams-Beuren syndrome.

METHODS

Study population

All adult (≥18 years) patients with SVAS who were prospectively registered in the Congenital Cor Vitia (CONCOR) database between 2001 and 2019 in all six Dutch expertise centres for CHD were included. CONCOR is a longitudinal registry that collects clinical data on adults with CHD in the Netherlands. SVAS was defined as either an hourglass obstruction or a diffuse stenosis involving the ascending aorta confirmed on echocardiography. Additionally, a fibrous diaphragm in the aortic lumen distal to the coronaries was also considered as SVAS. SVAS severity (gradient) was not considered an inclusion or exclusion criterium. However, patients with transposition of the great arteries or single outlet heart disease were excluded due to fundamental differences in aortic anatomy and haemodynamics. Follow-up for the current study started at the outpatient clinic visit 1 year before or after inclusion in CONCOR. This visit marked the beginning of the current study's follow-up, with data collection of survival and cardiovascular events ending June 2024. Patients and the public were not involved in the design or plans of this research.

Data collection and definitions

All data were collected retrospectively from the electronic patient files and were stored in a data capture programme Castor (Castor EDC V.2020.2). Relevant patient characteristics at first visit, repeated echocardiographic parameters and outcomes (ie, cardiovascular events and survival) were collected. Repeated echocardiographic evaluations were collected until SVAS-related (re)-intervention, if applicable, whereas survival data were collected continuously. Patients with prior ascending aortic replacement were excluded from repeated echocardiographic LVOT measurements. Williams-Beuren syndrome was defined as Williams-Beuren syndrome described in patients' history, diagnosed according to the centres' protocol. Definitions of the collected variables, their percentage of missing and cardiovascular events are listed in online supplemental file 1.

Functional class was reported according to the New York Heart Association classification in adults.[19]

Outcomes

Primary outcomes included all-cause mortality and SVAS-related (re)-intervention. Causes of death were classified as cardiac, non-cardiac or unknown. Recurrent cardiovascular events were categorised into heart failure, arrhythmic events, thromboembolic events, treated aortic aneurysm, acute aortic dissection, endocarditis, coronary events, SVAS-related (re)-intervention and other cardiac surgery and interventions. All postoperative events (<30 days postoperative) were excluded. Secondary outcomes included peak velocity evolution over time and event-free survival defined as a composite endpoint of mortality, heart failure, arrhythmic events, thromboembolic events, SVAS-related (re)-intervention, treated aortic aneurysm, acute aortic dissection, endocarditis, coronary events and other cardiac surgery. As a sensitivity analysis, arrhythmic events were excluded.

Statistical analyses

Continuous data are presented as means±SDs (Gaussian) or medians with an IQR (non-Gaussian). Categorical data are presented as counts with percentage. The Shapiro-Wilk test was used to assess Gaussian distribution. Comparisons between continuous variables were made with the unpaired t-test or the Mann-Whitney U test, as appropriate (two groups). For categorical variables, the χ^2 or Fisher's exact test (≤5 observations) was used for comparisons between groups. Baseline characteristics and outcomes were stratified by SVAS operation before inclusion (operative state at baseline (operated cohort/unoperated cohort)), sex (male/female) and Williams-Beuren syndrome (patients with/without Williams-Beuren syndrome). All statistical analyses were performed in R Statistical Software (Rstudio V.2022.07.2 and R Software V.4.2.2) with the use of packages survival, nlme and lme4. A p-value of $p<0.05$ was considered statistically significant.

Table 1 Patient characteristics of adult patients with supravalvular aortic stenosis, stratified by previous operated state, sex and Williams-Beuren syndrome

	Overall (N=65)	Unoperated cohort (N=35)	Operated cohort (N=30)	P value (U/O)	Male (N=45)	Female (N=20)	P value (M/F)	Non-Williams-Beuren (N=36)	Williams-Beuren (N=29)	P value (NWB/WB)
Age (years)	23.0 (20.0, 31.0)	24.0 (20.0, 28.5)	23.0 (19.3, 33.0)	0.658	23.0 (20.0, 31.0)	24.0 (19.0, 29.0)	0.943	22.0 (19.0, 28.5)	26.0 (20.0, 33.0)	0.260
Age at surgery (years)	8.7 (6.1, 12.5)	–	8.7 (6.1, 12.5)	–	6.9 (4.4, 12.3)	10.2 (7.2, 12.5)	0.244	9.6 (6.0, 12.3)	8.6 (6.6, 12.6)	0.722
Female (n)	20 (30.8)	6 (17.1)	14 (46.7)	**0.021**	–	20 (100.0)	**<0.001**	10 (27.8)	10 (34.5)	0.755
Height (metres)	169.1 (10.4)	171.9 (10.0)	165.7 (10.1)	**0.023**	172.8 (9.5)	160.3 (6.4)	**<0.001**	172.3 (10.7)	164.9 (8.4)	**0.005**
Weight (kg)	67.4 (14.6)	66.9 (13.8)	67.8 (15.6)	0.828	68.5 (12.6)	65.1 (18.2)	0.448	72.3 (14.2)	60.5 (12.3)	**0.004**
BMI (kg/m2)	23.2 (20.3, 25.1)	21.1 (19.7, 23.5)	24.1 (21.8, 26.0)	**0.027**	22.3 (20.3, 24.5)	23.3 (20.7, 28.9)	0.255	22.9 (20.9, 25.2)	23.2 (18.2, 24.2)	0.326
BSA (m2)	1.8 (0.2)	1.8 (0.2)	1.8 (0.2)	0.542	1.8 (0.2)	1.7 (0.2)	**0.046**	1.9 (0.2)	1.7 (0.2)	**<0.001**
Bicuspid aortic valve (n)	12 (18.5)	5 (14.3)	7 (23.3)	0.513	8 (17.8)	4 (20.0)	1.000	11 (30.6)	1 (3.4)	**0.019**
Stenosis at other LVOT level										
Valvular stenosis (n)	14 (21.5)	7 (20.0)	7 (23.3)	0.751	11 (24.4)	3 (15.0)	0.161	13 (36.1)	1 (3.4)	0.920
Subvalvular stenosis (n)	6 (9.2)	2 (5.7)	4 (13.3)	0.867	3 (6.7)	3 (15.0)	0.596	5 (13.9)	1 (3.4)	1.000
Concomitant CHD										
ASD (n)	4 (6.2)	1 (2.9)	3 (10.0)	0.498	2 (4.4)	2 (10.0)	0.763	4 (11.1)	0 (0.0)	0.182
VSD (n)	6 (9.2)	3 (8.6)	3 (10.0)	1.000	3 (6.7)	3 (15.0)	0.544	5 (13.9)	1 (3.4)	0.310
Patent ductus arteriosus (n)	3 (4.6)	–	3 (10.0)	0.186	1 (2.2)	2 (10.0)	0.460	2 (5.6)	1 (3.4)	1.000
Valvular pulmonary stenosis (n)	5 (7.7)	2 (5.7)	3 (10.0)	0.857	3 (6.7)	2 (10.0)	1.000	1 (2.8)	4 (13.8)	0.235
Peripheral pulmonary stenosis (n)	12 (18.5)	5 (14.3)	7 (23.3)	0.537	8 (17.8)	4 (20.0)	1.000	9 (25.0)	3 (10.3)	0.233
Tetralogy of Fallot (n)	1 (1.5)	1 (2.9)	0 (0.0)	1.000	1 (2.2)	0 (0.0)	1.000	1 (2.8)	0 (0.0)	1.000
Coarctatio aortae (n)	7 (10.8)	2 (5.7)	5 (16.7)	0.308	5 (11.1)	2 (10.0)	1.000	5 (13.9)	2 (6.9)	0.616
Aortic aneurysm (n)	3 (4.6)	1 (2.9)	2 (6.7)	0.891	3 (6.7)	0 (0.0)	0.588	2 (5.6)	1 (3.4)	1.000
Treated aneurysm (n)	1 (1.5)	–	1 (3.3)	1.000	1 (2.2)	0 (0.0)	–	1 (2.8)	0 (0.0)	1.000
Genetical disorders										
Williams-Beuren (n)	29 (44.6)	16 (45.7)	13 (43.3)	1.000	19 (42.2)	10 (50.0)	0.755	0 (0.0)	29 (100.0)	**<0.001**
Down syndrome (n)	2 (3.1)	1 (2.9)	1 (3.3)	1.000	2 (4.4)	0 (0.0)	0.857	1 (2.8)	1 (3.4)	1.000
Other genetic disorder (n)	3 (4.6)	–	3 (10.0)	0.186	1 (2.2)	2 (10.0)	0.460	3 (8.3)	0 (0.0)	0.319
Intellectual disability (n)	17 (26.2)	6 (17.1)	11 (36.7)	0.128	9 (20.0)	8 (40.0)	0.200	2 (5.6)	15 (51.7)	**<0.001**
Smoking										
Never (n)	32 (49.2)	14 (40.0)	18 (60.0)	0.277	21 (46.7)	11 (55.0)	1.000	17 (47.2)	15 (51.7)	0.085
Past (n)	3 (4.6)	1 (2.9)	2 (6.7)	1.000	2 (4.4)	1 (5.0)	1.000	3 (8.3)	0 (0.0)	0.428
Current (n)	7 (10.8)	6 (17.1)	1 (3.3)	0.098	5 (11.1)	2 (10.0)	1.000	6 (16.7)	1 (3.4)	0.320
Systemic arterial hypertension (n)	8 (12.3)	3 (8.6)	5 (16.7)	0.541	4 (8.9)	4 (20.0)	0.396	0 (0.0)	8 (27.6)	**0.003**
Diabetes (n)	1 (1.5)	1 (2.9)	0 (0.0)	1.000	1 (2.2)	0 (0.0)	1.000	0 (0.0)	1 (3.4)	0.913
Hyperlipidaemia (n)	2 (3.1)	1 (2.9)	1 (3.3)	1.000	1 (2.2)	1 (5.0)	1.000	2 (5.6)	0 (0.0)	0.546

Continued

Table 1 Continued

	Overall (N=65)	Unoperated cohort (N=35)	Operated cohort (N=30)	P value (U/O)	Male (N=45)	Female (N=20)	P value (M/F)	Non-Williams-Beuren (N=36)	Williams-Beuren (N=29)	P value (NWB/WB)
Previous interventions										
Previous subvalvular intervention (n)	2 (3.1)	–	2 (6.7)	1.000	0 (0.0)	2 (10.0)	1.000	2 (5.6)	0 (0.0)	1.000
Previous valvular intervention (n)	7 (10.8)	1 (2.9)	6 (20.0)	0.033	5 (11.1)	2 (10.0)	1.000	6 (16.7)	1 (3.4)	1.000
Previous supravalvular intervention (n)	30 (46.2)	–	30 (100.0)	**<0.001**	16 (35.6)	14 (70.0)	**0.021**	17 (47.2)	13 (44.8)	1.000
McGoon (n)	10 (15.4)	–	10 (33.3)	–	6 (13.3)	4 (20.0)	1.000	8 (22.2)	2 (6.9)	0.119
Doty (n)	6 (9.2)	–	6 (20.0)	–	4 (8.9)	2 (10.0)	0.861	2 (5.6)	4 (13.8)	0.455
Brom (n)	3 (4.6)	–	3 (10.0)	–	2 (4.4)	1 (5.0)	0.916	1 (2.8)	2 (6.9)	0.849
Sliding plasty (n)	1 (1.5)	–	1 (3.3)	–	0 (0.0)	1 (5.0)	1.000	0 (0.0)	1 (3.4)	0.916
Other (n)	6 (9.2)	–	6 (20.0)	–	1 (2.2)	5 (25.0)	0.095	2 (5.6)	4 (13.8)	0.455
Previous other cardiac surgery (n)	14 (21.5)	6 (17.1)	8 (26.7)	0.530	7 (15.6)	7 (35.0)	0.152	10 (27.8)	4 (13.8)	0.289
Symptoms at first visit (n)	22 (33.8)	14 (40.0)	8 (26.7)	0.385	13 (28.9)	9 (45.0)	0.326	11 (30.6)	11 (37.9)	0.718
NYHA class										
I (n)	56 (86.2)	30 (85.7)	26 (86.7)	1.000	40 (88.9)	16 (80.0)	1.000	32 (88.9)	24 (82.8)	0.632
II (n)	1 (1.5)	1 (2.9)	0 (0.0)	1.000	1 (2.2)	0 (0.0)	1.000	1 (2.8)	0 (0.0)	1.000
III (n)	1 (1.5)	0 (0.0)	1 (3.3)	0.944	0 (0.0)	1 (5.0)	0.647	1 (2.8)	0 (0.0)	1.000
IV (n)	–	–	–	–	–	–	–	–	–	–
Medication use*										
Blood pressure										
Systolic pressure (mm Hg)	138.3 (18.1)	139.4 (15.7)	137.0 (20.8)	0.606	139.0 (16.6)	136.6 (21.8)	0.639	136.9 (17.4)	140.2 (19.2)	0.497
Diastolic pressure (mm Hg)	76.4 (12.1)	78.6 (10.8)	73.8 (13.2)	0.123	76.6 (12.7)	75.9 (10.9)	0.843	74.3 (13.4)	79.2 (9.7)	0.120

*Online supplemental file 3 for additional details for medication use stratified by previous operated state, sex and Williams-Beuren syndrome.
ASD, atrial septal defect; BMI, body mass index; BSA, body surface area; CHD, congenital heart disease; COPD, chronic obstructive pulmonary disease; LVOT, left ventricular outflow tract; NYHA, New York Heart Association; VSD, ventricular septal defect.

Table 2 Echocardiographic measurements, electrocardiographic parameters and laboratory values at first visit of adult patients with supravalvular aortic stenosis, stratified by previous operated state, sex and Williams-Beuren syndrome

	Overall (n=65)	Unoperated cohort (n=35)	Operated cohort (n=30)	P value (U/O)	Male (n=45)	Female (n=20)	P value (M/F)	Non-Williams-Beuren (n=36)	Williams-Beuren (n=29)	P value (NWB/WB)
Echocardiographic parameters at first visit										
LVOT diameter (mm)	21.6 (1.7)	21.48 (1.79)	21.73 (1.70)	0.809	22.26 (1.37)	19.67 (0.58)	0.011	21.75 (1.67)	–	–
Indexed LVOT diameter (mm/m^2)	11.71 (0.98)	11.50 (1.05)	11.96 (0.95)	0.468	11.49 (0.88)	12.30 (1.20)	0.246	11.58 (0.92)	–	–
LVOT peak velocity (m/s)	1.0 (0.9, 1.2)	1.0 (0.9, 1.0)	1.1 (0.9, 1.4)	0.234	1.0 (0.9, 1.0)	1.3 (1.1, 1.4)	0.057	1.0 (1.0, 1.3)	0.9 (0.8, 0.9)	**0.011**
LVOT VTI (cm)	22.9 (5.0)	24.7 (4.0)	21.5 (5.4)	0.286	22.6 (5.4)	24.4 (0.5)	0.666	24.8 (4.0)	17.1 (2.3)	**0.010**
Aortic valve mean gradient (mm Hg)	11.0 (3.6, 18.0)	19.0 (8.2, 21.4)	8.0 (3.3, 15.5)	**0.031**	13.50 (3.95, 19.68)	9.60 (4.25, 15.50)	0.605	17.7 (10.7, 20.7)	3.6 (3.0, 6.2)	**0.001**
Aortic valve peak velocity (m/s)	2.3 (1.0)	2.3 (0.9)	2.0 (1.0)	**0.049**	2.40 (1.0)	2.06 (1.0)	0.261	2.7 (1.0)	1.8 (0.8)	**<0.001**
Aortic valve VTI (cm)	45.2 (21.2)	53.8 (22.0)	39.8 (19.6)	0.145	48.6 (23.7)	38.2 (14.1)	0.299	56.6 (17.9)	26.6 (10.0)	**<0.001**
Heart valves										
Aortic valve stenosis ≥ moderate (n)	10 (15.4)	8 (22.9)	2 (6.7)	0.158	8 (17.8)	2 (10.0)	0.597	9 (25.0)	1 (3.4)	0.116
Aortic valve regurgitation ≥ moderate (n)	6 (9.2)	2 (5.7)	4 (13.3)	0.699	5 (11.1)	1 (5.0)	0.647	4 (11.1)	2 (6.9)	0.837
Mitral valve stenosis ≥ moderate (n)	–	–	–	–	–	–	–	–	–	–
Mitral valve regurgitation ≥ moderate (n)	3 (4.6)	0 (0.0)	3 (10.0)	0.212	2 (4.4)	1 (5.0)	1.000	2 (5.6)	1 (3.4)	1.000
Tricuspid valve regurgitation ≥ moderate (n)	4 (6.2)	1 (2.9)	3 (10.0)	0.579	2 (4.4)	2 (10.0)	0.855	2 (5.6)	2 (6.9)	1.000
Tricuspid regurgitation velocity (m/s)	2.6 (0.4)	2.5 (0.2)	2.6 (0.5)	0.699	2.54 (0.57)	2.64 (0.32)	0.675	2.57 (0.51)	2.62 (0.31)	0.856
Left ventricular ejection fraction (%)	55.0 (9.7)	55.4 (6.4)	54.2 (15.7)	0.884	52.42 (10.16)	57.50 (9.95)	0.502	50.9 (9.4)	61.7 (6.7)	0.138
Systolic left ventricular function										
Normal (n)	55 (84.6)	30 (85.7)	25 (83.3)	0.876	37 (82.2)	18 (90.0)	1.000	30 (83.3)	25 (86.2)	1.000
Mildly impaired (n)	4 (6.2)	2 (5.7)	2 (6.7)	1.000	3 (6.7)	1 (5.0)	1.000	3 (8.3)	1 (3.4)	0.755
Moderately impaired (n)	1 (1.5)	0 (0.0)	1 (3.3)	0.946	0 (0.0)	1 (5.0)	0.721	0 (0.0)	1 (3.4)	0.919
Severely impaired (n)	–	–	–	–	–	–	–	–	–	–
ECG parameters										
ECG heart rhythm (n)										
Sinus rhythm (n)	61 (93.8)	34 (97.1)	27 (90.0)	0.867	43 (95.6)	18 (90.0)	0.473	34 (94.4)	27 (93.1)	0.867
Atrium fibrillation (n)	1 (1.5)	0 (0.0)	1 (3.3)	0.924	0 (0.0)	1 (5.0)	0.683	0 (0.0)	1 (3.4)	0.924
Atrial rhythm (n)	1 (1.5)	1 (2.9)	0 (0.0)	1.000	1 (2.2)	0 (0.0)	1.000	0 (0.0)	1 (3.4)	0.924
Paced rhythm (n)	1 (1.5)	0 (0.0)	1 (3.3)	0.924	0 (0.0)	1 (5.0)	0.683	1 (2.8)	0 (0.0)	1.000

Continued

Table 2 Continued

	Overall (n=65)	Unoperated cohort (n=35)	Operated cohort (n=30)	P value (U/O)	Male (n=45)	Female (n=20)	P value (M/F)	Non-Williams-Beuren (n=36)	Williams-Beuren (n=29)	P value (NWB/WB)
Heart rate (bpm)	70.0 (64.0, 82.0)	70.0 (65.0, 87.5)	73.0 (60.0, 79.0)	0.741	73.0 (63.8, 86.5)	70.0 (65.5, 77.0)	0.554	66.0 (57.5, 78.3)	76.0 (68.0, 86.0)	**0.010**
PR interval (Ms)	144.0 (136.5, 160.0)	144.0 (135.0, 151.5)	150.0 (138.0, 162.0)	0.376	144.0 (138.0, 160.0)	140.0 (128.0, 159.0)	0.216	146.0 (136.0, 160.0)	140.0 (138.0, 157.0)	0.487
QRS interval (Ms)	101.0 (90.0, 110.0)	98.0 (90.0, 104.5)	102.0(94.0, 114.0)	0.165	104.0 (93.5, 114.0)	94.0 (90.0, 102.0)	**0.024**	102.0 (90.5, 110.0)	100.0 (88.0, 108.0)	0.318
Left bundle branch block (n)	1 (1.5)	0 (0.0)	1 (3.3)	0.819	1 (2.2)	0 (0.0)	1.000	1 (2.8)	0 (0.0)	1.000
Right bundle branch block (n)	3 (4.6)	2 (5.7)	1 (3.3)	1.000	2 (4.4)	1 (5.0)	1.000	3 (8.3)	0 (0.0)	0.819

ECG, electrocardiography; LVOT, Left ventricular outflow tract; VTI, Velocity time integral.

Long-term outcomes

The Kaplan-Meier estimator was used to present long-term survival and event-free survival. To investigate differences in previous operated state, sex and Williams-Beuren syndrome in survival and event-free survival, the log-rank test was used. Follow-up completeness for survival was calculated with the Modified Clark's C method.[20]

Recurrent outcomes

Recurrent cardiovascular events are presented as adverse event rates (AERs/1000 patient years) and were calculated using the number of observed events and the total number of patient years multiplied by 1000. AERs were calculated for previous operated state, sex and Williams-Beuren syndrome. Comparisons in subgroups were made by using the two-sided mid-p exact test.[21] As a sensitivity analysis, cardiovascular events were also determined in patients with isolated SVAS; this concerns patients without other concomitant CHD (including bicuspid aortic valve or secondary LVOT obstructions).

Repeated measures

Maximum peak velocity of the entire LVOT trajectory (peak velocity) over time was analysed using linear mixed models (online supplemental 2). Random effects were explored to see if patients showed fast progression (>0.3 m/s/year).[9]

RESULTS

Patients and first visit

In total, 65 patients (31% female) were included with a median age of 23 (IQR: 20–31) years. Of these, 28% were diagnosed with SVAS during adulthood (n=18, mean age 25 years). Williams-Beuren syndrome was diagnosed in 45% (n=29) of the patients. In total, 24 patients of the total cohort (37%) had an isolated SVAS. In total, 57% had undergone some form of cardiac surgery prior to inclusion, including SVAS repair or surgery for other CHD and 46% of the patients (n=30) had undergone SVAS repair before inclusion. The median age at primary SVAS correction before inclusion was 9 (IQR: 6–13) years. The proportion of females was significantly larger in the operated cohort compared with the unoperated cohort (47% vs 17%, p=0.021). Baseline characteristics stratified by previous operated state, sex and Williams-Beuren syndrome are listed in table 1 and table 2.

All-cause mortality

Follow-up completeness was 84% for survival. Median follow-up time was 13 (IQR: 10–17) years. During 804 patient years, four patients died (one patient died after cardiac surgery, two patients died of non-cardiac causes and in one patient the cause of death was unknown). More details of the causes of death and patient characteristics are shown in online supplemental 4. Kaplan-Meier estimate for survival at 10 years was 95% (95% CI 90% to 100%) (figure 1)

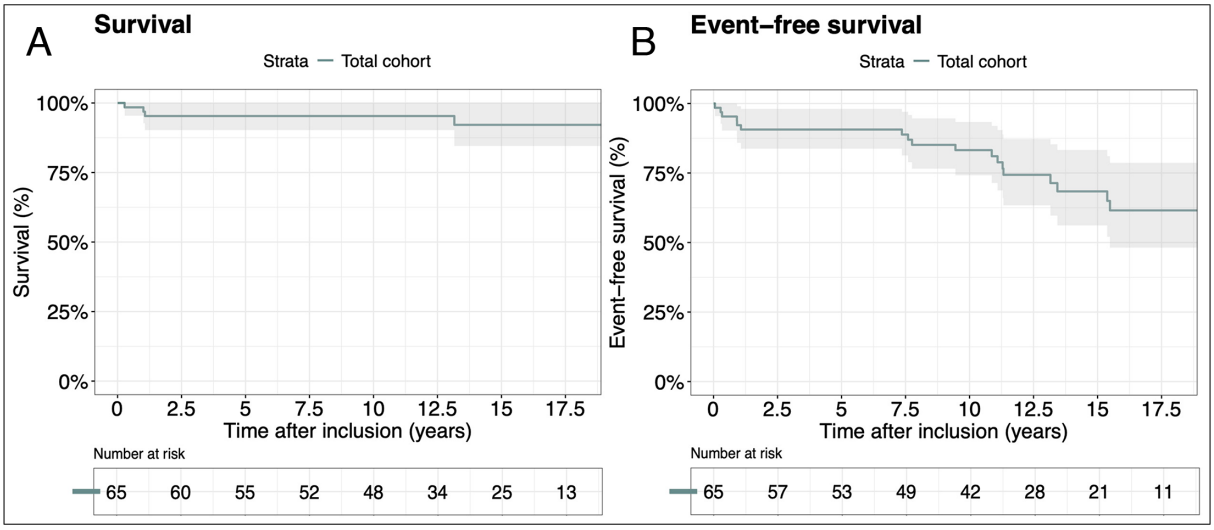

Figure 1 Kaplan-Meier estimates for (A) survival and (B) event-free survival for all patients (n=65).

and for the operated cohort and unoperated cohort 97% (95% CI 91% to 100%) and 94% (95% CI 94% to 87%), respectively (online supplemental 5). It was not possible to calculate the log-rank test to compare survival within the groups because of too few events.[22] Of the 24 patients (314 patient years) with an isolated SVAS, one patient died during follow-up due to a non-cardiac cause.

Cardiovascular events

Event-free survival

In total, 31 events occurred in 15 different patients. The 10-year event-free survival was 83% (95% CI 74% to 93%) (figure 1) and for the operated and unoperated cohort 79% (95% CI 65% to 96%) and 87% (95% CI 76% to 100%), respectively (p=0.200) (figure 2). No significant differences in event-free survival were observed between males/females (p=0.480) and presence of Williams-Beuren syndrome (p=0.850) (figure 2). As a sensitivity analysis, the arrhythmic events were excluded in the Kaplan-Meier estimates for event-free survival for the total cohort and for the comparison of previous operated state (online supplemental 6). Still no significant differences in event-free survival were observed in previous operated state (p=0.360). In patients with isolated SVAS, only three events occurred in three patients (one SVAS-related intervention and two arrhythmic events).

Cardiac and SVAS (re)-intervention

During follow-up, six surgical cardiac interventions were performed in five patients (online supplemental 7). Of these interventions, three were related to the SVAS, of which two out of three were performed in relation to concomitant LVOT obstruction. All SVAS-related surgeries were performed in the unoperated cohort with an AER for SVAS-related intervention of 7 (95% CI 2 to 21)/1000 patient years. In the operated cohort, no SVAS-related reintervention occurred. Of the three SVAS-related interventions that were performed during follow-up, one intervention was performed in a patient with an isolated SVAS. One cardiac endovascular intervention was performed during follow-up; this included stenting of the left and right pulmonary artery to relieve peripheral pulmonary stenosis.

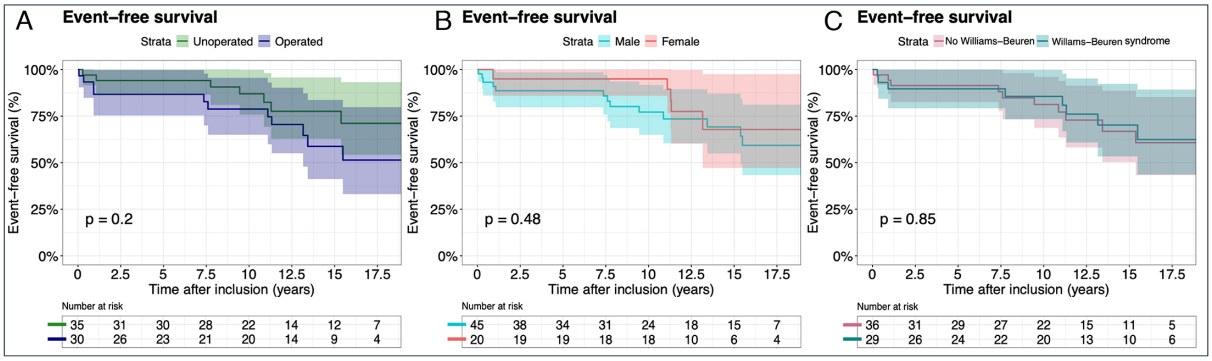

Figure 2 Kaplan-Meier estimates for event-free survival, stratified by (A) previous operated state (operated n=35, unoperated n=30), (B) sex (males n=45, females n=20) and (C) Williams-Beuren syndrome (Williams-Beuren syndrome n=36, non-Williams-Beuren syndrome n=29).

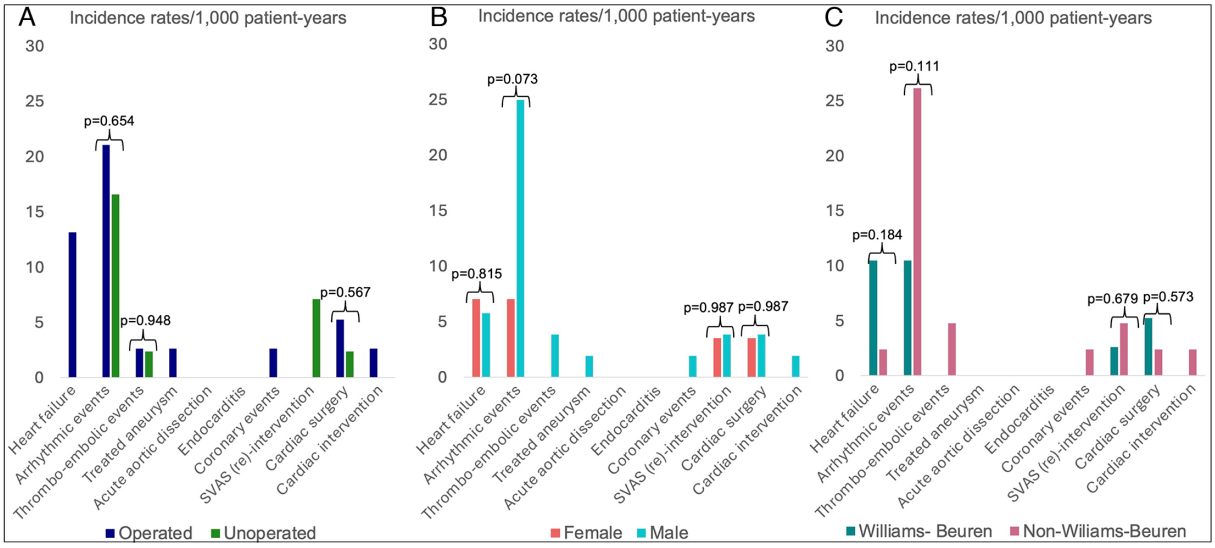

Figure 3 Incidence rates of the cardiovascular events in the different subgroups (A) previous operated state, (B) sex and (C) Williams-Beuren syndrome.

Other cardiac events

Figure 3 shows the incidence rates of cardiovascular events per subgroup. 15 arrhythmic events occurred in eight patients, of which the majority was atrial fibrillation (eight events). The AER for arrhythmic events was 21 (95% CI 9 to 42)/1000 patient years in the operated cohort and 17 (95% CI 7 to 34)/1000 patient years for the unoperated cohort (p=0.65). Heart failure occurred in three patients, all in the operated cohort, with an AER of 13 (95% CI 4 to 31)/1000 patient years. During total follow-up, one coronary event occurred in a male patient of 47 years old, known with hyperlipidaemia, which was treated with a percutaneous coronary intervention. A summary of the secondary events is listed in online supplemental 7 and 8.

Evolution of peak velocity

In total, 320 (±6 per patient) echocardiographic evaluations were analysed. Coefficients of the linear mixed model are provided in online supplemental 9. The peak velocity remained stable over time with no significant change in peak velocity (first spline: −0,4 m/s, p=0.080, second spline: −0.2 m/s, p=0.428). There was no significant difference in peak velocity between the operated and unoperated cohort (first time spline: −0.3 m/s, p=0.289; second time spline: -0.5, p=0.117). Patients with Williams-Beuren syndrome had significantly lower start peak velocity compared with patients without (p<0.001). Peak velocity progression was significantly faster in females compared with males (first time spline: 0.8 m/s, p=0.017). Figure 4 shows the evolution of the peak velocity in different subgroups. Looking at the random effects of the linear mixed model, no patient showed fast progression (≥0.3 m/s/year). Online supplemental 10 shows the subject-specific trajectories.

DISCUSSION

This study presents 13 years of follow-up data on adult patients with SVAS who were followed in all six tertiary care centres specialised in CHD in the Netherlands. To the best of our knowledge, this is the first study conducting linear mixed models for repeated measurements on echocardiographic evaluations for this patient group. In addition, differences in several subgroups and their intersections were evaluated. While overall peak velocities remained stable within the normal range, women showed a trend towards faster progression. All SVAS-related operations occurred in the unoperated group, implying that if a patient already underwent surgery for SVAS, a reintervention in adulthood was not observed. Cardiovascular events did occur, but overall survival was good. Among patients with isolated SVAS (37% of the total cohort), very few events were observed during follow-up.

Patient presentation

Overall, adult patients with SVAS presented in stable clinical condition, regardless of SVAS-related surgery in early life. The mean gradient at inclusion was ~19 mm Hg in the unoperated cohort and ~8 mm Hg in the operated cohort, in line with prior studies.[23] Of patients, 46% had undergone surgical repair of SVAS before inclusion (at a median age of 9 years), which was lower compared with another study which reported 67%.[15] This may imply a less diseased patient population in the current study. However, it can also be the result of practice variation in timing for operation during childhood. Additionally, more than half of the patients in our cohort presented with a concomitant heart anomaly, underlining that patients with SVAS represent a heterogeneous population. This may have influenced the observed event rates as well.

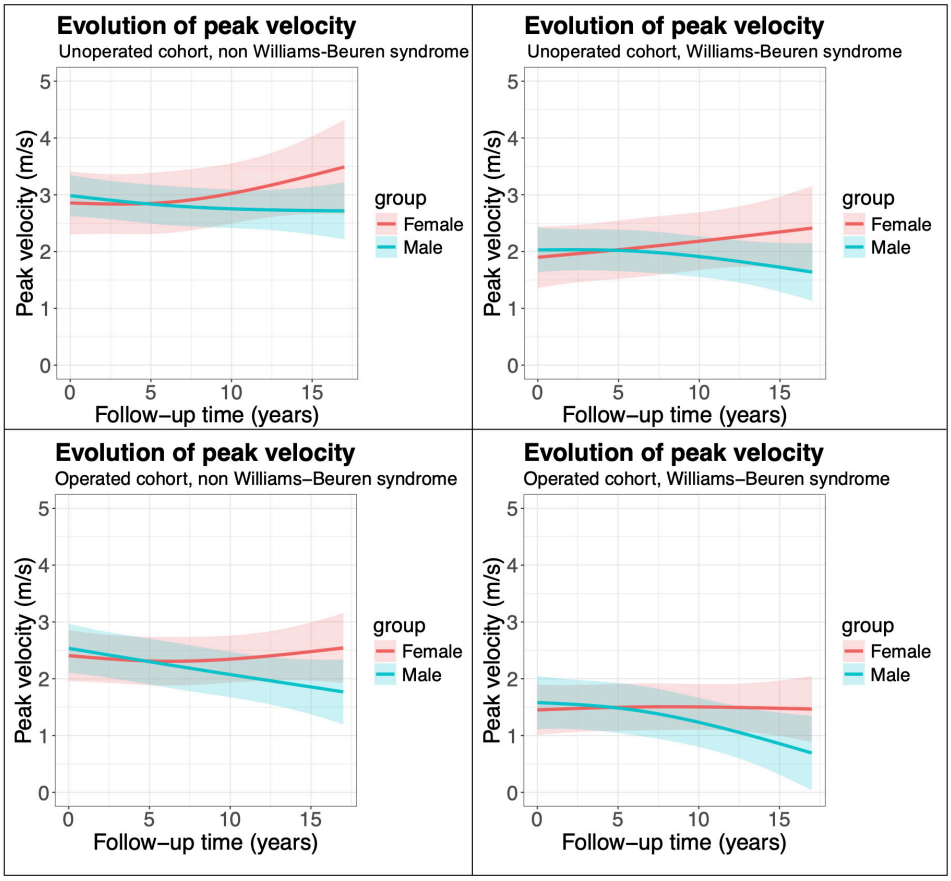

Figure 4 Effect plots of peak velocity evolution for different subgroups (previous operated state, sex and Williams-Beuren syndrome). Predictions based on: Williams-Beuren + operated n=13, non-Williams-Beuren + operated n=17, Williams-Beuren + unoperated n=16, non-Williams-Beuren + unoperated n=19.

Survival

In the current study, the 10-year survival was 95%, consistent with prior studies.[15 24] This indicates that if a patient with SVAS survives until adulthood, long-term survival is promising with a benign disease course. However, caution is needed when interpreting these results for a young patient population, as outcomes beyond early adulthood remain unknown. Although previous studies reported the risk of cardiac events and sudden cardiac death in patients with SVAS,[25 26] only one cardiac death occurred in our cohort, attributed to post-operative heart failure. Many physicians are concerned about cardiac and sudden unexplained deaths resulting from coronary events due to the high-pressure conditions of the coronary circulation in patients with SVAS.[16] However, in our study, no sudden cardiac deaths were observed, although one cause of death was unknown. This means that these concerns could not be confirmed or denied with our data.

SVAS-related (re)-intervention

Of the three SVAS-related surgeries performed during follow-up, two were performed in relation to concomitant LVOT obstruction. A condition known to be associated with increased risk of late mortality and SVAS-related reintervention.[24 27 28]

In another adult cohort, SVAS-related (re)-intervention occurred in 4% of the patients, comparable to our cohort.[15] Notably, in the current study, none of the patients who needed surgery for SVAS before inclusion required reintervention in adulthood. This contrasts with Meccanici *et al*,[10] who reported a reintervention rate of ~30% in their systematic review consisting of studies reporting outcomes after SVAS correction. The discrepancy may be due to differences in the age at surgery (5 years vs 9 years in our study) and surgical techniques, with nearly half of Meccanici *et al*'s patients undergoing the McGoon technique, compared with a broader range of techniques in our cohort. Additionally, it seems that most events after SVAS surgery typically occur within 15 years, a period not captured in our cohort, with a median age at surgery of 9 years and a median age at inclusion of 23 years. A similar trend was observed in another Dutch cohort, where most events occurred within the first 10–15 years postsurgery (median age at surgery 8 years).[29] This may help explain the limited number of reinterventions and deaths in our cohort compared with other studies.

Other cardiovascular events

Cardiovascular events occurred in 23% (15/65) of the adults with SVAS, mainly driven by arrhythmic events. 60% of the total cohort had undergone any cardiac

surgery before inclusion. Repaired (congenital) cardiac lesions and cardiac scar tissue are a source of re-entry circuits and can increase the risk of arrhythmic events.[30] This may potentially explain why most events in this cohort were arrhythmic events, with the majority of the arrhythmic events being atrial fibrillation. Rhythm monitoring with electrocardiography should be considered at every follow-up visit in all patients.

It is stated that attention should be given to coronary events in adult patients with SVAS as the coronaries are subject to increased pressure and impaired flow due to the SVAS.[16] In our study, one coronary event occurred during follow-up in a 47-year-old male patient, also known with hyperlipidaemia. It is unclear whether this coronary event was related to the SVAS, to the hyperlipidaemia or the combination. Especially since the anatomical features of the coronary lesion were unknown. In children, ostial coronary lesions in patients with SVAS are typically caused by the abnormal growth of the aortic root.[31] It may be that this mechanism is not present anymore in the adult population, also since another study on adults with SVAS reported no coronary events.[15] The fear of acquired atherosclerotic coronary disease also becomes more relevant in adulthood.[32] No evidence was found that coronary tomography (CT) would be needed to screen these patients. Currently, we only recommend performing CT in case of symptoms. Larger studies are needed to provide better insights into the risk factors of coronary events in patients with SVAS.

Peak velocity progression

No patient in the current study exhibited rapid disease progression. While previous reports suggest that progression can occur, our data confirms it is less common in adults than in children.[7 8] A study reporting on children showed a significant time-related increase in peak gradient of 11.3 mm Hg,[7] whereas studies reporting on adults showed stable gradients.[33] Differences in the evolution of the stenosis in children and adults may be explained by the aetiology of the SVAS obstruction. Although the cause of SVAS remains largely unknown, the elastin gene plays a role.[4 5] SVAS may also be the result of differential growth of the aortic root during bodily growth and is not the result of degenerative tissue changes, progressive tissue ingrowth or hyperplasia.[34] Therefore, it may be that such a lesion is progressive in childhood but remains stable in adults, once the (differential) growth of the root is completed.[15] Our study provides evidence for this relatively benign course during adulthood.

Patient-specific risk factors

Only three events in three patients were observed during follow-up in the group of patients with isolated SVAS. This implies that most events occurred in patients with concomitant heart disease. Moreover, it is known that (sub)valvular aortic stenosis as an additional source of LVOT obstruction can expose the left ventricle to high pressures, resulting in heart failure and arrhythmias.[10] This underlines the need to focus on concomitant cardiac (congenital) anomalies for optimal disease management in adult patients with SVAS, but at the same time results in a more optimistic view regarding the impact of the SVAS itself. However, further investigation in larger cohorts is needed to draw more generalisable conclusions.

In our study, the proportion of women was larger in the operated cohort compared with the unoperated cohort. Additionally, the peak velocity progressed significantly faster in women compared with men. This was more pronounced in unoperated women compared with unoperated men. This potentially suggests that women may experience a more aggressive form of the disease, potentially requiring earlier SVAS intervention. However, in both groups, the progression was mild, and the clinical implications seem therefore limited. Another study found that aortic stenosis is more common in women compared with men with bicuspid aortic valve (although bicuspid valve is more common in men).[35] This may be due to sex-related differences in the pathophysiological mechanisms of the disease progression of aortic stenosis, which also could explain why the disease tends to be more aggressive in women observed in the current study.

Patients with Williams-Beuren syndrome appear to have lower peak velocities at baseline compared with those without. This may imply earlier diagnosis or earlier surgical treatment in these patients. No significant differences in outcomes were observed in patients with Williams-Beuren syndrome compared with patients without, as reported in other studies.[10] Although patients with Williams-Beuren syndrome are known to have abnormal cardiac repolarisation,[36] there was no significant difference in arrhythmias observed between patients with and without Williams-Beuren syndrome. More research is needed on the long-term outcomes and complications of elastin mutations, as these might be more important for follow-up schedules than the (mild) progression of SVAS itself. Larger cohort studies with multivariable models are necessary to identify predictors of rapid disease progression and high-risk patients with SVAS and elastin mutations.

Limitations

Although patients received prospective follow-up, data collection and analyses were performed retrospectively. Therefore, limitations inherent to this type of research are present. Referral bias may be present as all six Dutch expertise centres for CHD participated in this study, but no local hospitals participated. There may be practice variation between the centres in follow-up duration and imaging protocols. The diagnosis of Williams-Beuren syndrome with genetic testing may differ per centre. Therefore, a standardised clinical testing procedure for Williams-Beuren syndrome is not guaranteed. Genetic testing results for ELN pathogenic variants were not consistently collected and represent a limitation.

Peak velocity of the LVOT trajectory, measured with continuous wave, was used for the linear mixed model,

assumed valid for 78% of the patients without secondary LVOT stenosis. However, a sensitivity analysis excluding secondary LVOT stenosis showed no change in model coefficients. Additionally, echocardiographic Doppler gradients can either overestimate or underestimate the severity of SVAS due to various factors, such as LV systolic dysfunction and the type of stenosis (whether tubular or discrete). Patients with SVAS represent a heterogeneous population, potentially influencing observed outcomes. The event rates should be interpreted in this light. Because of the small sample size and few events, it was not possible to conduct (multivariable) models to determine risk factors associated with cardiac events, to determine outcomes after different surgical techniques or to calculate the log-rank test to compare the Kaplan-Meier estimates for survival between subgroups. Instead, we chose to stratify the cohort by clinically relevant subgroups—such as Williams-Beuren syndrome status, sex and prior SVAS surgery—to explore patterns and highlight differences in subgroups, acknowledging the limitations of this approach. Statistical correction for missing data (eg, multiple imputation) was not applied. A power issue may be present in the stratified analyses.

CONCLUSION

In contrast to children, adults with SVAS present clinically stable and show excellent 10-year survival. While cardiovascular events occur, they are mostly seen in patients with concomitant CHD, suggesting a more optimistic view for SVAS itself. No significant differences in outcomes were observed in patients with/without Williams-Beuren syndrome. Women showed faster disease progression than men, which was more pronounced in unoperated patients; this potentially might imply a more aggressive disease course in women. However, overall, if patients with SVAS survive into adulthood, they generally experience a benign disease course with slow progression of SVAS, suggesting that less frequent follow-up may be sufficient. However, follow-up should remain individualised, considering associated heart defects and the risk of other cardiovascular events.

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Funding This study was conducted in light of the Congenital Aortic Stenosis in Adults (CASIA) study within the OUTREACH consortium funded by the Dutch Heart Foundation and Hartekind Foundation.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval The protocol for this study was reviewed and approved by the local medical ethics committees (MEC-2021–0169). At inclusion in the CONCOR database, patients provided written informed consent to make their cardiologic follow-up data available for research purposes.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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