The clinical course and outcomes of supravalvular aortic stenosis in adults

SUPPLEMENTARY MATERIALS

Supplement 1. Collected variables, their definitions and percentage missing for baseline variables.

Supplement 2. Supplementary methods, details regarding linear mixed-effects model analysis

Supplement 3. Additional details for medication use stratified by previous operated state, sex and Williams-Beuren.

Supplement 4. Causes of death and patient characteristics of the deceased patients

Supplement 5. Kaplan- Meier estimates for survival, stratified by A) previous operated state, B) sex and C) Williams-Beuren.

Supplement 6. Kaplan- Meier estimates for event-free survival excluding arrhythmic events, A) all patients and B) previous operated state.

Supplement 7. Summary of all events that occurred during follow-up of adult patients with SVAS.

Supplement 8. Adverse event rates (AER)/ 1,000 patient years of collected cardiovascular events, stratified by previous operated state, including p-value.

Supplement 9. Coefficients of linear mixed model for peak velocity (m/s) progression.

Supplement 10. Plot of subject specific predictions of the linear mixed model for peak velocity (m/s).

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Supplement 1.

Collected data	%Missing	Definition
Year of birth	0%	Year of birth
Age at time of surgery	0%	Age at time of primary SVAS surgery before inclusion, in years
Sex	0%	Male or female
Height	8%	Height as described at first visit, in meters
Weight	26%	Weight at first visit, in kilograms
Body mass index	26%	Body mass index, in kg/m2
Body surface area	26%	Body surface area using Du Bois formula, in m2
Bicuspid valve	9%	Bicuspid aortic valve described or confirmed by echocardiography
Secondary stenosis present	0%	Valvular and/or subvalvular stenosis present besides the primary supravalvular stenosis at first visit
Concomitant congenital heart abnormalities	0%	Atrial septal defect, ventricular septal defect, patent ductus arteriosus, valvular pulmonary stenosis, peripheral pulmonary stenosis, tetralogy of Fallot or other congenital heart defects present at first visit or described in patient history
Prior coarctatio aortae	0%	Coarctatio aortae present at first visit or described in patient history
Treated coarctatio aortae	0%	
Prior aneurysm aortae	0%	If the aorta was measured ≥40 millimetre at level of the aortic root, STJ, and/or ascending aorta at first visit or described in patient history
Treated aneurysm	0%	
Genetically disorders	0%	Williams-Beuren, Noonan syndrome, Down syndrome, Marfan syndrome or other genetically disorders at first visit or described in patient history
Mental retardation	3%	A form of mental retardation is described in the patient history
Family history of congenital heart defects	62%	1st and 2nd degree relatives with a congenital heart disease at first visit. No cardiomyopathies.
Family history of cardiovascular disease	48%	1st degree relative with cardiovascular disease before the age of 55 for men and before the age of 65 for women relatives at first visit
Smoking	36%	Never, past = from >1 package year in patient history, currently smoking at first visit
History of hypertension	0%	Medical treatment and/or diagnosis of hypertension in patient history at first visit
History of diabetes mellitus	0%	Medical treatment and/or diagnosis of diabetes mellitus in patient history at first visit

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History of hyperlipidaemia	6%	Medical treatment and/or diagnosis of hyperlipidaemia in patient history at first visit
Previous cardiac surgery	0%	Prior cardiac surgery at first visit
Previous subvalvular intervention	0%	Prior intervention indicated for the subvalvular stenosis at first visit
Previous valvular intervention	0%	Prior intervention indicated for a valvular stenosis at first visit
Previous supravalvular intervention	0%	Prior intervention indicated for a supravalvular stenosis at first visit
Prior cardiac myopathy	0%	Hypertrophy or dilated at first visit
Symptoms at first visit	0%	Any symptoms reported at first visit
NYHA classification	11%	New-York Heart Association classification at first visit. NYHA I: no symptoms; NYHA II: symptoms during extensive physical activity; NYHA III: symptoms during physical activity; NYHA IV: symptoms during few or no physical activity, at rest
Medication use at first visit	6%	Medication use at first visit; none, beta-blocker, ACE inhibitor, diuretics, anti-arrhythmic medication, calcium channel blockers, vitamin K antagonists, platelet inhibitors, angiotensin receptor blockers, other medication
Echocardiography definitions		
Left ventricular systolic function	8%	Left ventricular function as described in the echocardiography report at first visit; in % and categorized in normal, mildly impaired, moderately impaired, or severely impaired
Aortic stenosis	28%	Aortic stenosis as described. Grade: 1/3 or ¼ = mild; 2/3, 2/4, ¾ = moderate; 3/3 or 4/4 = severe
Aortic regurgitation	12%	Aortic regurgitation as described. Grade: 1/3 or ¼ = mild; 2/3, 2/4, ¾ = moderate; 3/3 or 4/4 = severe
Mitral stenosis	17%	Mitral stenosis as described. Grade: 1/3 or ¼ = mild; 2/3, 2/4, ¾ = moderate; 3/3 or 4/4 = severe
Mitral regurgitation	11%	Mitral regurgitation as described. Grade: 1/3 or ¼ = mild; 2/3, 2/4, ¾ = moderate; 3/3 or 4/4 = severe
Tricuspid regurgitation	12%	Tricuspid regurgitation as described. Grade: 1/3 or ¼ = mild; 2/3, 2/4, ¾ = moderate; 3/3 or 4/4 = severe
Left ventricular outflow tract diameter	82%	Left ventricular outflow tract diameter at first visit echocardiography, in mm
Left ventricular outflow tract peak velocity	59%	Peak velocity at level of the left ventricular outflow tract at first visit echocardiography, in m/s
Aortic valve mean gradient	55%	Mean gradient of the aortic valve at first visit echocardiography, in mmHg
Aortic valve peak velocity	17%	Peak velocity at level of the aortic valve at first visit echocardiography, in m/s
Aortic valve VTI	68%	Aortic valve VTI at first visit echocardiography, in cm
Left ventricular outflow tract VTI	82%	Left ventricular outflow tract VTI at first visit echocardiography, in cm

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Tricuspid regurgitation velocity	77%	Peak velocity of tricuspid valve at first visit echocardiography, in m/s
ECG definitions		
Heart rate	3%	Heart rate at first visit, in beats per minute (bpm)
PR-interval	17%	PR interval at first visit, in Ms
QRS	14%	QRS duration at first visit, in Ms
QT-time	36%	QT-time at first visit, in Ms
QTc-time	34%	QTc-time at first visit, in Ms
Bundle branch block	0%	QRS > 120 Ms. RBTB, if QRS positive in V1, LBTB, if negative in V1 at first visit
Signs of LVH	48%	Description of cardiologist in ECG report, or clear signs of LVH on ECG at first visit
ST-segment changes	29%	Description of cardiologist in ECG report or clear signs on ECG at first visit
Blood pressure	6%	BP in mmHg as measured at first visit. When patient with coarctatio aortae or two measurements: BP from right arm
Clinical outcomes		
Deceased during follow-up		Deceased between time of start study and date of last mortality check
Cause of death		Cardiac or non-cardiac cause of death
Heart failure		Development or worsening of heart failure, start or increase in diuretics or hospitalization needed
Arrhythmic events		Symptomatic and ECG registered or treatment was needed
Thrombo-embolic event		Cerebrovascular accident, lung embolism, myocardial infarction, systemic embolism
Intervention for subvalvular stenosis		If secondary subvalvular stenosis was present
Intervention for valvular stenosis		If secondary valvular stenosis was present
Intervention for supravalvular stenosis		SVAS related intervention or reintervention
Endocarditis		Endocarditis during follow-up
Thoracic aortic aneurysm		Measured at admittance or maximum 1y before surgery , >40 millimetres at level of the aortic root, STJ, and/or ascending aorta,
Thoracic aortic dissection		Acute type A or type B dissection during follow-up
Hospitalization for other cardiac reason		Measured at admittance, or maximum 1y before surgery
Other cardiac surgery or intervention		Cardiac surgery or intervention not indicated for a LVOT obstruction

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Supplement 2.

Maximum peak velocity of the entire LVOT trajectory (peak velocity) over time was analysed using linear mixed models. Natural cubic splines were added for time to allow for non-linear (flexible), subject-specific trajectories over time. The final covariates included in the models were: time, previous supravalvular intervention, sex, Williams-Beuren syndrome and interactions time*(previous supravalvular intervention+ sex+ Williams-Beuren syndrome). Interaction terms were used to investigate the relative effect in the different subgroups. The number of knots for the cubic splines in the random-effects and fixed-effects parts were determined using a backwards selection approach. Comparisons between models were made with likelihood ratio tests, if appropriate. After model selection, within the random-effects part, the non-linear effect of time using 2 cubic splines proved to be sufficient in the model for peak velocity.

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Supplement 3.

Medication use	Overall (N=65)	Unoperated cohort (N=35)	Operated cohort (N=30)	P-value	Male (N=45)	Female (N=20)	P-value	Non-Williams-Beuren (N=36)	Williams-Beuren (N=29)	P-value
None (n)	43 (66.2)	26 (74.3)	17 (56.7)	0.098	31 (68.9)	12 (60.0)	0.588	26 (72.2)	17 (58.6)	0.638
β-blocker (n)	4 (6.2)	1 (2.9)	3 (10.0)	0.535	1 (2.2)	3 (15.0)	0.161	0 (0.0)	4 (13.8)	0.060
ACE inhibitor (n)	2 (3.1)	0 (0.0)	2 (6.7)	0.429	1 (2.2)	1 (5.0)	1.000	1 (2.8)	1 (3.4)	1.000
Diuretics (n)	3 (4.6)	1 (2.9)	2 (6.7)	0.930	1 (2.2)	2 (10.0)	0.470	1 (2.8)	2 (6.9)	0.791
Anti-arrhythmics (n)	2 (3.1)	1 (2.9)	1 (3.3)	1.000	2 (4.4)	0 (0.0)	0.849	2 (5.6)	0 (0.0)	0.608
Calcium channel blockers (n)	1 (1.5)	0 (0.0)	1 (3.3)	0.960	1 (2.2)	0 (0.0)	1.000	0 (0.0)	1 (3.4)	0.880
Vitamin K antagonists (n)	1 (1.5)	0 (0.0)	1 (3.3)	0.960	0 (0.0)	1 (5.0)	0.681	0 (0.0)	1 (3.4)	0.880
Platelet inhibitors (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
Angiotensin receptor blockers (n)	2 (3.1)	0 (0.0)	2 (6.7)	0.429	1 (2.2)	1 (5.0)	1.000	0 (0.0)	2 (6.9)	0.346
Other medication (n)	6 (9.2)	2 (5.7)	4 (13.3)	0.577	2 (4.4)	4 (20.0)	0.130	5 (13.9)	1 (3.4)	0.358

Legend: ACE, angiotensin-converting enzyme

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Supplement 4.

	Cause of death	**Patient characteristics**
Patient 1	Respiratory insufficiency with hypercapnic coma	- 40 years old - Female - No other congenital anomalies - Mental retardation - Williams syndrome - Operated cohort
Patient 2	Post-operative heart failure after Bentall procedure for a degenerating homograft	- 36 years old - Male - Bicuspid valve - Homograft implantation (Mediastinitis) and re-valvulotomy aortic valve - Operated cohort
Patient 3	Unknown	- 33 years old - Male - Absent left carotid artery - Williams syndrome - Unoperated cohort
Patient 4	Haemolytic streptococcus bacteria with sepsis	- 26 years old - Male - ASD - Peripheral pulmonary stenosis - Prior cardiac surgery - Unoperated cohort

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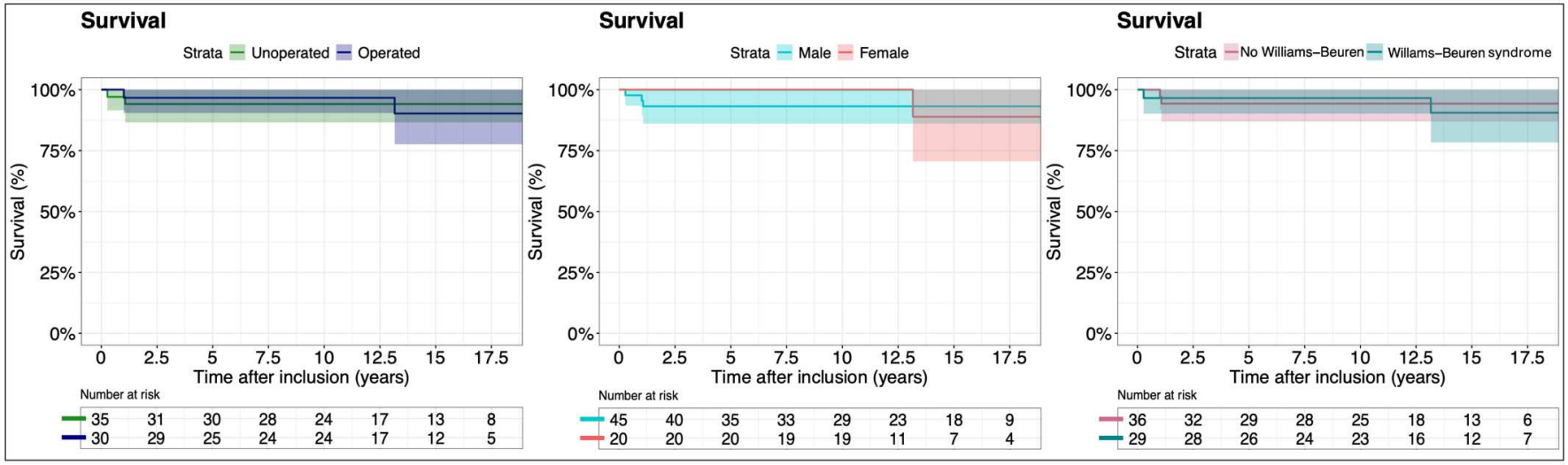
Supplement 5.



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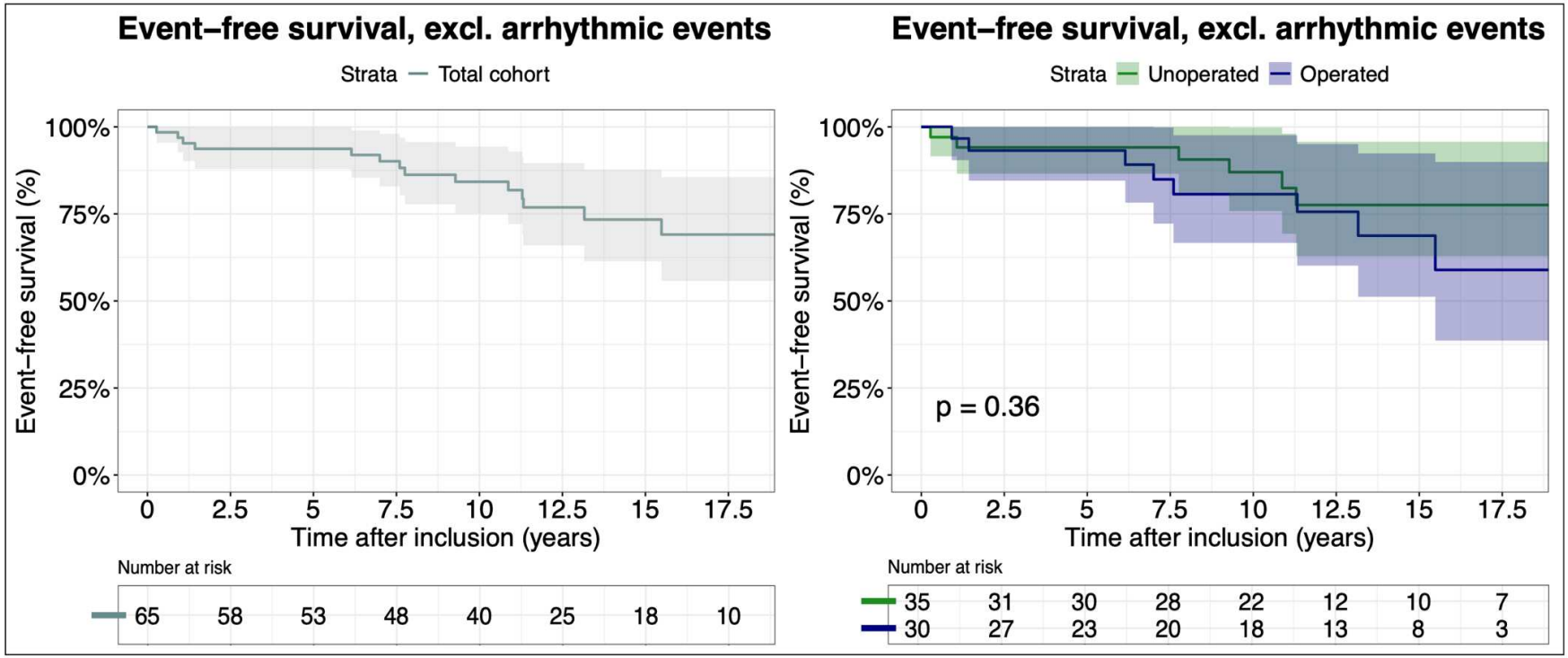
Supplement 6.



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Supplement 7.

Event	Type of event	Treatment or comment
Heart failure (5 events in 3 patients)	Heart failure	Medication
	Heart failure	Medication
	Heart failure	Medication
	Heart failure	Medication
	Heart failure	Medication
Arrhythmic events (15 events in 8 patients)	Atrial fibrillation	Electrical cardioversion
	Atrial fibrillation	Pulmonary vain isolation ablation
	Atrial fibrillation	Electrical cardioversion
	Atrial fibrillation	Electrical cardioversion
	Atrial fibrillation	Re- pulmonary vain isolation ablation
	Atrial fibrillation	Spontaneous cardioversion before planned electrical cardioversion
	Atrial fibrillation	Medication
	Ventricular fibrillation	Out of hospital cardiac arrest due to coronary event
	Atrial fibrillation	Medication
	VT/SVT	Medication
	VT/SVT	Medication
	Atrial tachycardia	Medication
	Atrial flutter	Medication
	AV block	Pacemaker implantation
	AVRNT	AVRNT ablation
Thrombo- embolic events (2 events in 2 patients)	Pulmonary embolism	
	DVT	After craniotomy
Treated aneurysm (1 event in 1 patient)	Ascending aortic dilatation 54mm	Aortic valve replacement + supra-coronary aortic replacement
Acute aortic dissection	-	-
Endocarditis	-	-
Coronary event (1 event in 1 patient)		Percutaneous coronary intervention, stent in left anterior descending artery
SVAS related (re-)intervention (3 events in 2 patients)		Ross-procedure
		Aortic valve replacement + aortic replacement
		T. David procedure
Cardiac surgery (3 events in 3 patients)		Mitral valve repair + two neo chordae + Tricuspid valve repair
		Aortic valve replacement with biological prosthesis due to aortic regurgitation
		Aortic valve replacement with mechanical prosthesis due to aortic regurgitation
Cardiac intervention (1 event in 1 patient)		Stent in left pulmonary artery and right pulmonary artery

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Supplement 8.

	Operated cohort			**Unoperated cohort**			**[Operated/Unoperated]**
	Number of events during follow-up	Total patient years	Adverse event rate/1,000 patient years	Number of events during follow-up	Total patient years	Adverse event rate/1,000 patient years	P-value
Heart failure	5	380	13.2 (4.3-30.7)	-	422	-	-
Arrhythmic events	8	380	21.1 (9.1-41.5)	7	422	16.6 (6.7-34.2)	0.654
Thrombo- embolic events	1	380	2.6 (0.1-14.7)	1	422	2.4 (0.1-13.2)	0.948
Treated aneurysm	1	380	2.6 (0.1-14.6)	-	-	-	-
Acute aortic dissection	-	-	-	-	-	-	-
Endocarditis	-	-	-	-	-	-	-
Coronary event	1	380	2.7 (0.1-14.8)	-	-	-	-
SVAS related (re-)intervention	-	-	-	3	422	7.1 (1.5-20.8)	-
Cardiac surgery	2	380	5.3 (0.7-19.0)	1	422	2.4 (0.1-13.2)	0.567
Cardiac intervention	1	380	2.6 (0.1-14.6)	-	-	-	-

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Supplement 9.

	Linear mixed model for peak velocity (in m/s)	
	Coefficient (m/s)	**P-value**
Intercept	3.0	<0.001
Time (time spline 1)	-0.4	0.080
Time (time spline 2)	-0.2	0.428
Prior supravalvular intervention before inclusion	-0.5	0.052
Female	-0.2	0.561
Williams- Beuren syndrome	-0.9	<0.001
Time (time spline 1)*Prior supravalvular intervention before inclusion	-0.3	0.289
Time (time spline 2)*Prior supravalvular intervention before inclusion	-0.5	0.117
Time (time spline 1)*Female	0.8	0.017
Time (time spline 2)*Female	0.8	0.018
Time (time spline 1)*Williams- Beuren syndrome	0.1	0.639
Time (time spline 2)*Williams-Beuren syndrome	-0.2	0.570

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Supplement 10.