Surgical Outcome of Discrete Subaortic Stenosis in Adults:
A Multicenter Study

Running title: Van der Linde et al.; Discrete subaortic stenosis in adults

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Abstract:

**Background**—Discrete subaortic stenosis (DSS) is notable for its unpredictable hemodynamic progression in childhood and high re-operation rate, however data about adulthood are scarce.

**Methods and Results**—Adult patients who previously underwent surgery for DSS were included in this retrospective multicenter cohort study. Mixed-effects and joint models were used to assess postoperative progression of DSS and aortic regurgitation (AR), and re-operation. A total of 313 patients at 4 centers were included (age at baseline 20.2 years (Q1 to Q3, 18.4-31.0), 52% male). Median follow-up duration was 12.9 years (Q1 to Q3, 6.2-20.1), yielding 5617 patient-years. The peak instantaneous left ventricular outflow tract (LVOT) gradient decreased from 75.7±28.0 mmHg pre-operatively to 15.1±14.1 mmHg postoperatively (p<0.001), and thereafter increased over time at a rate of 1.31±0.16 mmHg per year (p=0.001). Mild AR was present in 68%, but generally did not progress over time (p=0.76). A pre-operative LVOT gradient ≥80 mmHg was a predictor for progression to moderate AR postoperatively. Eighty patients required at least one re-operation (1.8% per patient-year). Predictors for re-operation included female gender (HR=1.53, 95%CI 1.02-2.30) and LVOT gradient progression (HR=1.45, 95%CI 1.31-1.62). Additional myectomy did not reduce the risk for re-operation (p=0.92), but significantly increased the risk of a complete heart block requiring pacemaker implantation (8.1% versus 1.7%; p=0.005).

**Conclusions**—Survival is excellent after surgery for DSS, however reoperation for recurrent DSS is not uncommon. Over time the LVOT gradient slowly increases and mild AR is common, though generally nonprogressive over time. Myectomy does not show additional advantages and as it is associated with an increased risk of complete heart block, it should not be performed routinely.

**Key words:** echocardiography, heart defects, congenital, risk factor, aortic stenosis, surgery
Introduction

Discrete subaortic stenosis (DSS) is notable for its unpredictable and sometimes rapid hemodynamic progression in childhood and its association with aortic regurgitation (AR), which is found in 30-80% of patients. Different strategies exist for the timing of surgical treatment, ranging from early (mild to moderate obstruction) to late (severe or symptomatic) repair. Early repair has been advocated to prevent aortic valve damage and thus AR progression. Nevertheless, it remains unclear whether surgery can actually alter the course of progressive AR. Furthermore, surgery is associated with a high recurrence risk and need for re-operation (8-34%). A major factor in DSS recurrence is believed to be inadequate relief of the obstruction. Therefore some groups advocate concomitant selective myectomy to achieve complete relief of the LVOT obstruction, whereas others have reported that the addition of myectomy does not reduce the number of recurrences.

While postoperative outcome and risk factors for re-operation in children are well established, postoperative data for the adult population are limited. Therefore, the aim of this study was to identify risk factors for postoperative DSS recurrence, AR progression and re-operation in a large cohort of adult patients who previously underwent surgical treatment for DSS.

Methods

All adult patients who previously underwent surgery for fibromuscular DSS and were seen between January 1980 and October 2011 at the Congenital Cardiac Center for Adults of one of the participating centers (Erasmus University Medical Center, Rotterdam, and Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands; University Hospital
Gasthuisberg, Leuven, Belgium; and Toronto Congenital Cardiac Centre for Adults located at Peter Munk Cardiac Centre, Toronto, Canada) were evaluated for eligibility for this study.

Fibromuscular DSS was defined as a complete or incomplete encirclement of the LVOT by a membrane or short-segment stenosis consisting of fibrous or fibromuscular tissue. Baseline of this study was defined as time of first adult outpatient clinic visit. Eligible patients were selected from the CONCOR database (the Dutch registry for adult patients with congenital heart disease (CHD)), and from the Leuven and Toronto local database for adults with CHD. Although all patients followed in Congenital Cardiac Centers for Adults were ≥17 years old, the first surgery for DSS could have been performed in childhood. Exclusion criteria were: lack of serial echocardiograms, non-DSS causes for subaortic obstruction (tunnel-like subaortic narrowing, hypertrophic cardiomyopathy, accessory mitral valve tissue or mitral valve prosthesis), concomitant moderate-to-severe valvular aortic stenosis, transposition of the great arteries and univentricular connections. This retrospective study was approved by the institutional review board and ethical committee of participating centers. Informed consent was waived.

Demographic, clinical and surgical data were obtained from medical charts and electronic health records. All available transthoracic echocardiograms, electrocardiograms and exercise tests were collected. Peak systolic instantaneous LVOT gradient was derived from the continuous wave Doppler LVOT peak flow velocity. The degree of AR was graded by experienced echocardiographers and cardiologists as mild, moderate, or severe. Left ventricular mass was calculated using the modified-Devereux-formula. In the parasternal long-axis view at end-diastole, we measured the aorto-septal angle, which is the angle formed by the plane of the ventricular septum and the ascending aorta, as previously described.
Statistical analysis

The Statistical Package for Social Sciences, version 19.0 (SPSS, Inc., Chicago, Illinois) was used for descriptive data-analysis. Continuous variables were summarized using mean ± standard deviation (SD) and median and 25th percentile (Q1) to 75th percentile (Q3). Categorical variables were summarized using the frequency and percentage. The paired t-test, paired Wilcoxon and McNemar’s test were used to compare pre- and postoperative measurements. All statistical tests with a p-value <0.05 were considered significant.

For advanced statistical analyses of the longitudinal and survival data, the R statistical software (version 2.15.0, available at: www.r-project.org) was used. To assess changes in echocardiographic measurements over time while accounting for the correlation between repeated follow-up measurements in each patient, mixed-effects models analyses were used. In particular, for the postoperative LVOT gradient progression rate a linear mixed-effects model was used, whereas for postoperative AR progression a mixed-effects continuation ratio model was employed. To allow for flexibility in the modeling of the patient-specific longitudinal trajectories, we used natural cubic splines of time in the specification of the mixed-effects models, both in the fixed- and random effect part of the models. The following variables were included in the models as covariates: age at time of surgery, age at diagnosis, gender, preoperative peak instantaneous LVOT gradient, difference between pre- and postoperative gradient (delta), type of surgery (isolated enucleation or additional myectomy), associated CHD and smoking. For each of the covariates in the model its main effect and interaction with time was added, allowing for different average longitudinal evolutions per covariate. Residual plots were used to validate the models’ assumptions, and when appropriate transformations of the outcome variables were used in the analysis. Furthermore, to account for missing covariate data a multiple
imputation approach was used for the covariates pre- and postoperative LVOT gradient (missing for 42 patients). Five generations of ‘complete’ data sets were realized. Wald tests were used to assess which prognostic factors were most associated with the progression of peak instantaneous LVOT gradient and AR.

Probabilities of intervention-free survival from baseline were obtained by the Kaplan-Meier method. Survival of DSS patients was compared to the expected survival of the age-matched normal Dutch population. Patients were censored at end of follow-up or classified as event (surgery for DSS or death). A penalized likelihood approach was employed for the Cox regression model with baseline data, to account for the low number of events compared to the number of covariates. A joint longitudinal and survival model and the time-dependent Cox model were respectively used to investigate the effect of peak instantaneous LVOT gradient and AR on the hazard ratio (HR) for intervention-free survival.

Results

A total of 737 patients were assessed for eligibility to participate in this study. Inclusion criteria were met by 313 patients. Four hundred twenty-four patients were excluded, mainly due to LVOT obstruction due to another cause (n=145), no history of DSS surgery (n=149) or lack of serial echocardiography examinations (n=74).

Baseline characteristics of the 313 patients are summarized in Table 1. One hundred sixty-three patients (52.1%) had one or more associated CHD. Baseline LVOT diameter was 14.5±3.8 mm in women and 15.7±4.2 mm in men (p=0.19). Follow-up ranged from 1 to 31 years (median 12.9, Q1 to Q3 6.2-20.1 years), yielding a total of 5617 patient-years. On average 2.3 ± 1.4 (minimum 2, maximum 8) echocardiographic studies were available for each patient.
Operative outcomes

The 313 included patients underwent a total of 412 operations for DSS. The peak instantaneous LVOT gradient decreased from 75.7 ± 28.0 mmHg pre-operatively to 15.1 ± 14.1 mmHg postoperatively (p<0.001). The LVOT diameter increased from 14.5 ± 3.8 mm to 19.0 ± 3.7 mm (p<0.001). In 251 patients (61%) the first surgery was performed in childhood (mean age 12.9±6.7 years). Table 2 shows the surgical details, including concomitant surgery and postoperative complications. In those patients who did not undergo concomitant aortic valve repair or replacement during surgery for DSS, the severity of AR was unchanged postoperatively (p=0.60). Seventeen patients (4.4%) suffered from a complete heart block postoperatively, requiring pacemaker implantation. Patients who underwent an additional myectomy more frequently developed a complete heart block than patients who underwent isolated enucleation (respectively 8.1% versus 1.7%; p=0.005).

Mortality and morbidity

One death occurred within 30 days after surgery for DSS due to heart failure. Ten patients (mean age 49.1 ± 16.5 years) died during follow-up (0.18% per patient-year) (Figure 1A). Five deaths were for cardiac reasons (4 heart failure and 1 septic shock after endocarditis). In 2 patients the cause of death was metastasized cancer. Three patients died suddenly during follow-up (unknown cause of death, no autopsy; age 19, 30 and 48 years old, all had an LVOT gradient <30 mmHg at last follow-up visit, 2 had an associated ventricular septal defect, no left ventricular hypertrophy). The cumulative survival of DSS patients after surgery was 97% at 20 years.

During follow-up 34 patients (age 29.9 ± 15.1 years) were hospitalized for various reasons (0.61% per patient-year): heart failure (n=13), endocarditis (n=12), ventricular
fibrillation followed by successful resuscitation (n=2), cardioversion for atrial fibrillation (n=5), stroke (n=1) and pericarditis (n=1).

Re-operations

During follow-up, 80 patients (25.6%) underwent at least one re-operation for recurrent DSS, of whom 19 patients required a third operation (re-operation rate 1.76% per patient-year) (Table 2). The mean time interval between initial operation and re-operation was 12.0 ± 7.6 years. Median intervention-free survival was 17 years (Figure 1A). Independent predictors for impaired intervention-free survival were female gender (HR=1.531 (95%CI 1.018–2.302); Figure 1B), peak instantaneous LVOT gradient progression over time (HR=1.454 (95% CI 1.308–1.616)), pre-operative peak instantaneous LVOT gradient ≥80 mmHg (HR=1.016 (95% CI 1.004–1.028)) and difference between pre- and postoperative peak instantaneous LVOT gradient (HR=1.021 (95% CI 1.007–1.035)) (Online Supplement Table 1).

Recurrence of LVOT gradient postoperatively

Postoperative peak instantaneous LVOT gradient was 15.1 ± 14.1 mmHg, which linearly increased over time at a rate of 1.31 ± 0.16 mmHg per year (p=0.001). Independent risk factors for faster postoperative peak instantaneous LVOT gradient progression were increased age at time of DSS diagnosis (p=0.048) and female gender (p=0.059, trend) (Figure 2). A higher pre-operative LVOT gradient was associated with an overall higher residual postoperative peak instantaneous LVOT gradient (p<0.001), but did not significantly influence the postoperative peak instantaneous LVOT gradient progression rate (p=0.74). Peak instantaneous LVOT gradient progression rate was not influenced by type of surgery (enucleation +/- myectomy) (p=0.85), age at time of surgery (p=0.21), presence of associated CHD (p=0.12) or smoking (p=0.24) (Online Supplement Table 2).
Progression of AR postoperatively

Immediately postoperatively mild AR was present in 68% of patients and moderate AR in 5%, no patients exhibited severe AR. Over time, AR severity did not significantly progress in the total study population (p=0.76; Figure 3). Approximately 10% of patients, however, progressed from having no AR to mild AR, and another 10% of patients developed moderate AR during the first 8 years after surgery (Figure 3). None of the patients progressed to severe AR. A pre-operative peak instantaneous LVOT gradient ≥80 mmHg was an independent risk factor for development of moderate AR postoperatively (p=0.008; Figure 4). We could not identify any other factor that was significantly associated with postoperative development of mild AR or progressive AR (Online Supplement Table 3).

Discussion

In this multicenter study, we have analyzed data on a large cohort of adult patients who underwent surgical DSS resection with 13 years postoperative follow-up (range 1 to 31 years) to determine predictors for DSS recurrence, AR worsening and re-operation. The results of the present study may be the basis for modification of the current strategies for management of DSS patients.

DSS recurrence and re-operations

In the total study population, postoperatively the peak instantaneous LVOT gradient increased slowly, though significantly, over time with 1.3 mmHg per year. This finding confirms a smaller study that previously reported a slight increase in postoperative gradient at late follow-up.27 Surprisingly, increased age at time of diagnosis (>30 years old) was a risk factor for faster postoperative LVOT gradient progression. This phenomenon might be explained by the fact that

9
when DSS was discovered late in adulthood, patients were more likely to present with symptoms and thus might be in an advanced stage of the disease. Another hypothesis is that aging itself is related to faster postoperative progression.

In this study we used re-operation as an objective clinically relevant outcome, rather than recurrence only because of lack of a universal definition for recurrence. We do acknowledge that the indication for reoperation is also not concrete and universal. Our re-operation rate for recurrent DSS (1.8% per patient-year) was comparable to two other adult surgical series, which reported re-operation rates of 0.5% and 2.6% per patient-year.\textsuperscript{15,27} As reported in several studies in children with DSS, a higher peak instantaneous gradient across the LVOT at the final pre-operative echocardiogram was an independent predictor for re-operation in our adult patient population.\textsuperscript{10,12,16,17,24} Testing various cut-off points, we found that a peak instantaneous LVOT gradient $\geq 80$ mmHg is most predictive for the need of re-operation. In addition, incomplete removal of the LVOT obstruction, reflected in a smaller difference between pre- and postoperative gradient, was found to be a risk factor for re-operation. This has previously been demonstrated in several previous studies.\textsuperscript{12,15,20,22,26,37} Furthermore, as expected, LVOT gradient progression postoperatively is a strong predictor for re-operation. In addition to the echocardiographic parameters to monitor and predict LVOT gradient progression, perhaps biomarkers might be useful to identify those with more rapidly progressing disease. Further research in this area is warranted.

Surprisingly, women carry a 1.5 times elevated risk for re-operation compared to men. In addition, female patients tended to have a more rapid postoperative LVOT gradient progression rate than male patients. These gender differences in re-operation or recurrence risk have not been reported previously. This phenomenon might be explained by the fact that women are likely to
have a smaller LVOT. In our cohort the LVOT diameter tended to be smaller in women compared to men, although not statistically significant. Perhaps pregnancy might have been a confounding factor, but unfortunately we did not collect information about pregnancies during follow-up, and there is a lack of studies investigating the consequences of pregnancy in DSS patients. Furthermore, transcriptional regulation of genes related to myocardial hypertrophy and fibrosis might be gender dependent, as has been shown after aortic valve replacement for valvular aortic stenosis.\(^{38}\) Pathophysiological studies are required to explore the underlying mechanisms for these gender differences.

**Isolated enucleation versus additional myectomy**

Several hypotheses regarding DSS recurrence have been proposed. Recurrence may result from regeneration of tissue from the same region or from scar formation in the subvalvular area during healing.\(^{19,39}\) Furthermore, turbulence due to incomplete removal of the LVOT obstruction has been postulated to promote fibrosis and subsequent restenosis.\(^{12}\) Although some previous studies have suggested that additional myectomy during the first operation reduces the incidence of recurrence, other authors have questioned this finding.\(^{8,16-27}\) Our results do not support the benefit of additional myectomy, neither for the risk of re-operation, nor for the LVOT gradient progression rate postoperatively. A trade-off when performing aggressive surgical resection to potentially lower the recurrence rate is the risk of a complete AV-block, which was significantly higher in the patients who underwent additional myectomy compared to those who underwent isolated enucleation (8% versus 2%). In previous studies the risk of a postoperative complete AV-block is typically 1% to 5%, however this might be up to 14% when a more aggressive surgical approach is performed.\(^{6,7,12,17,20}\) Of course the results of a myectomy and risk of heart block are operator dependent, but this study included patients from four different centers over a
time span of 30 years making it impossible to study this factor adequately. Therefore, from our study we conclude that an additional myectomy may be justified when a substantial degree of septal hypertrophy is detected, but should be discouraged in the majority of patients.

**Aortic regurgitation after DSS surgery**

While most DSS patients exhibited mild (non hemodynamically relevant) AR both pre- and postoperatively, our study shows that in the majority of patients AR is not progressive over time. Approximately 10% of patients who did not have AR before, however, developed mild AR relatively shortly after surgery. Furthermore, another 10% of patients progressed from mild to moderate AR, but progression to severe AR was very rare. We identified a pre-operative peak instantaneous LVOT gradient ≥80 mmHg as a risk factor for progressive AR after surgery.

Previous studies in children with DSS have also demonstrated the association between a high pre-operative LVOT gradient and progressive AR postoperatively. In order to prevent progressive AR postoperatively, it may be wise to perform re-operation before the peak LVOT gradient reaches 80 mmHg. In conclusion, we agree with the statement made by Stassano et al. that resection of the subaortic membrane cannot improve AR, but we disagree with their suggestion that resection can entirely “stabilize” the grade of regurgitation.

**Clinical implications**

Postoperative long-term survival after surgical treatment of DSS is excellent and comparable to the normal population. The rate of reoperation is considerable (approximately 2% per year), and given the excellent survival of these young adult patients, the majority of patients will require a reoperation for recurrent DSS at some point in their life. Post-operatively the peak instantaneous LVOT gradient progresses slowly, though steadily, over time in adults. Therefore lifelong regular follow-up, including echocardiography, is required after surgery, but since the LVOT
progression is generally slow this can probably be limited to 2-4 year intervals in the majority of patients. Women and patients >30 years old at time of diagnosis are at risk for faster LVOT gradient progression after surgery, and should thus be monitored more frequently. Of course patients with decreased LV function or severe/progressive AR should also be followed more frequently. Additional myectomy did not reduce DSS recurrence or re-operation risk, and significantly increased the risk of a complete heart block. Therefore myectomy should not be encouraged in the majority of patients, and only be performed in case of marked LV hypertrophy. Postoperative AR is common, however generally mild and non-progressive over time in the majority of patients. Patients with a pre-operative Doppler derived peak instantaneous LVOT gradient ≥80 mmHg, however, are at increased risk for development of moderate AR, but progression to severe AR is rare.

The current ESC and ACC/AHA guidelines for adults with CHD do not provide specific recommendations for re-interventions in DSS patients. The Canadian guidelines state that a peak instantaneous LVOT gradient >50 mmHg is an indication for re-operation when patients have symptoms. The timing of re-operation is a highly complex issue that should take various factors into account: the peak LVOT gradient, progression rate of the LVOT gradient, severity and progression of AR, LV volume and function, the presence of (exercised induced) symptoms, and the risk of sudden death. Unfortunately, the optimal timing of re-operation, combining all these factors, in adult patients with DSS cannot yet be derived from the present study.

Study limitations

Several limitations of this study merit attention. This retrospective study included patients monitored in adult congenital clinics, and therefore referral bias may exist. One of the major study limitations was the fact that indications for (re-)operation were not standardized, because
of the multicenter approach and broad time period. By using prospective databases to identify eligible patients and therefore also including deceased patients, we aimed to limit survival bias. Unfortunately, some echocardiographic parameters could not be retrieved for all patients, but this was dealt with by using the multiple imputation approach for missing values. The fact that echocardiography was not performed precisely every year, was accounted for by the use of mixed-effects models that take different lengths of follow-up into account. Furthermore, by using the joint modeling approach we allowed for the dependency and association between the longitudinal echocardiographic data and survival data. Ideally, our findings need to be validated by a large prospective cohort study.

Conclusions

Although survival is excellent after surgery for DSS, the majority of patients will require a reoperation for recurrent DSS throughout life. Postoperatively the LVOT gradient progresses slowly and mild AR is common, but non-progressive over time in the majority of patients. Myectomy should not be performed routinely, since it does not reduce the risk of recurrence or re-operation and increases the risk of a complete heart block.

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Conflict of Interest Disclosures: None.
References:


Table 1. Baseline characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Operated DSS patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>163 (52.1)</td>
</tr>
<tr>
<td>Age at baseline, years</td>
<td>20.2 (18.4-31.0)</td>
</tr>
<tr>
<td>Age at DSS diagnosis, years</td>
<td>8.0 (4.0-15.0)</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>1.8 ± 0.2</td>
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<tr>
<td>Body mass index, kg/m²</td>
<td>25.9 ± 5.4</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>125.6 ± 19.4</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>72.6 ± 10.9</td>
</tr>
<tr>
<td>Associated CHD anomalies; previously repaired *</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>150 (47.9)</td>
</tr>
<tr>
<td>Ventricular septal defect</td>
<td>72 (23.0); 15 (4.8)</td>
</tr>
<tr>
<td>Atrial septal defect</td>
<td>18 (5.8); 4 (1.3)</td>
</tr>
<tr>
<td>Valvular aortic stenosis</td>
<td>29 (9.3); 2 (0.6)</td>
</tr>
<tr>
<td>Coarctation of the aorta</td>
<td>48 (15.3); 10 (3.2)</td>
</tr>
<tr>
<td>Persistent ductus arteriosus</td>
<td>20 (6.4); 8 (2.6)</td>
</tr>
<tr>
<td>Shone complex</td>
<td>10 (3.2); 0 (0.0)</td>
</tr>
<tr>
<td>Aortoseptal angle, °</td>
<td>124.7 ± 15.9</td>
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<tr>
<td>Left atrial diameter, mm (indexed for BSA, mm/m²)</td>
<td>42.4 ± 11.7 (22.8 ± 5.3)</td>
</tr>
<tr>
<td>Left ventricular mass, gram (indexed for BSA, mm/m²)</td>
<td>222.0 ± 86.3 (120.1 ± 42.8)</td>
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<tr>
<td>LV end-diastolic diameter, mm (indexed for BSA, mm/m²)</td>
<td>49.1 ± 7.5 (27.1 ± 4.4)</td>
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<tr>
<td>LV end-systolic diameter, mm (indexed for BSA, mm/m²)</td>
<td>29.5 ± 7.4 (16.3 ± 4.3)</td>
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<tr>
<td>LV fractional shortening, %</td>
<td>40.3 ± 9.0</td>
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<tr>
<td>E/A ratio</td>
<td>1.5 ± 0.6</td>
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<tr>
<td>E/E’ ratio</td>
<td>11.9 ± 6.0</td>
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<tr>
<td>Maximum exercise capacity, % from norm</td>
<td>82.1 ± 20.4</td>
</tr>
<tr>
<td>Sinus rhythm</td>
<td>295 (94.2)</td>
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<tr>
<td>Heart frequency, beats per minute</td>
<td>72.5 ± 14.5</td>
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<tr>
<td>QRS duration, ms</td>
<td>114.9 ± 28.9</td>
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<td>PR time, ms</td>
<td>160.5 ± 30.9</td>
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<td>NYHA class I</td>
<td>290 (92.9)</td>
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<tr>
<td>Smoking</td>
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<tr>
<td>Never</td>
<td>211 (67.4)</td>
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<tr>
<td>Former</td>
<td>26 (8.3)</td>
</tr>
<tr>
<td>Current</td>
<td>64 (20.4)</td>
</tr>
<tr>
<td>Unknown</td>
<td>12 (3.8)</td>
</tr>
</tbody>
</table>

Values are n(%), median (Q1 to Q3) or mean±SD.
* Diagnoses are not mutually exclusive.

BSA = body surface area; CHD = congenital heart disease; DSS = discrete subaortic stenosis; LV = left ventricular; LVOT = left ventricular outflow tract; NYHA = New York Heart Association.
Table 2. Surgical details for 412 DSS operations.

<table>
<thead>
<tr>
<th></th>
<th>First operation (n=313)</th>
<th>Second operation (n=80)</th>
<th>Third operation (n=19)</th>
</tr>
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<tbody>
<tr>
<td>Age at time of surgery, years</td>
<td>17.1 ± 14.9</td>
<td>22.9 ± 13.9</td>
<td>32.1 ± 10.4</td>
</tr>
<tr>
<td>Pre-operative peak LVOT gradient, mmHg</td>
<td>74.7 ± 28.9*</td>
<td>79.3 ± 22.2</td>
<td>76.6 ± 36.3</td>
</tr>
<tr>
<td>Postoperative peak LVOT gradient, mmHg</td>
<td>14.6 ± 13.8*</td>
<td>17.6 ± 16.2</td>
<td>10.9 ± 9.2</td>
</tr>
<tr>
<td>Pre-operative aortic regurgitation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>84 (26.8)</td>
<td>15 (18.8)</td>
<td>1 (5.3)</td>
</tr>
<tr>
<td>Mild</td>
<td>173 (55.3)</td>
<td>26 (32.5)</td>
<td>5 (26.3)</td>
</tr>
<tr>
<td>Moderate</td>
<td>44 (14.1)</td>
<td>15 (18.8)</td>
<td>4 (21.0)</td>
</tr>
<tr>
<td>Severe</td>
<td>12 (3.8)</td>
<td>24 (30.0)</td>
<td>9 (47.4)</td>
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<tr>
<td>Postoperative aortic regurgitation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>87 (27.8)</td>
<td>18 (22.5)</td>
<td>5 (26.3)</td>
</tr>
<tr>
<td>Mild</td>
<td>208 (66.4)</td>
<td>59 (73.8)</td>
<td>13 (68.4)</td>
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<td>Moderate</td>
<td>18 (5.8)</td>
<td>3 (3.8)</td>
<td>1 (5.3)</td>
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<tr>
<td>Severe</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Type of surgery</td>
<td></td>
<td></td>
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<tr>
<td>Isolated enucleation</td>
<td>189 (60.4)</td>
<td>31 (38.8)</td>
<td>8 (42.1)</td>
</tr>
<tr>
<td>Additional myectomy</td>
<td>122 (39)</td>
<td>43 (53.8)</td>
<td>9 (47.4)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (0.6)</td>
<td>6 (7.5)</td>
<td>2 (10.5)</td>
</tr>
<tr>
<td>Concomitant surgery †</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic valve bioprosthesis</td>
<td>8 (2.5)</td>
<td>7 (8.8)</td>
<td>2 (10.5)</td>
</tr>
<tr>
<td>Aortic valve mechanical prosthesis</td>
<td>10 (3.2)</td>
<td>12 (15.1)</td>
<td>8 (42.1)</td>
</tr>
<tr>
<td>Aortic valve repair</td>
<td>18 (5.8)</td>
<td>7 (8.8)</td>
<td>2 (10.5)</td>
</tr>
<tr>
<td>Ross procedure</td>
<td>2 (0.6)</td>
<td>12 (15.0)</td>
<td>2 (10.5)</td>
</tr>
<tr>
<td>Coarctation repair</td>
<td>4 (1.3)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Supravalvular aortic repair</td>
<td>3 (1.0)</td>
<td>1 (1.3)</td>
<td>1 (5.3)</td>
</tr>
<tr>
<td>Persistent ductus arteriosus ligation</td>
<td>9 (2.9)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Mitral valve replacement or repair</td>
<td>8 (2.5)</td>
<td>3 (3.8)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Ventricular septal defect closure</td>
<td>46 (14.7)</td>
<td>1 (1.3)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Atrial septal defect closure</td>
<td>6 (1.9)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Postoperative complications †</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New left bundle branch block</td>
<td>36 (3.2)</td>
<td>8 (10)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>New right bundle branch block</td>
<td>33 (3.2)</td>
<td>3 (3.8)</td>
<td>1 (5.3)</td>
</tr>
<tr>
<td>New complete heart block requiring pacemaker</td>
<td>12 (3.8)</td>
<td>3 (3.8)</td>
<td>2 (10.5)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>6 (1.9)</td>
<td>2 (2.5)</td>
<td>2 (10.5)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>3 (1.0)</td>
<td>1 (1.3)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Mortality</td>
<td>1 (0.3)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Neurological complication (stroke or neuropathy)</td>
<td>1 (0.3)</td>
<td>2 (2.5)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

Values are n(%) or mean±SD.
*Only available for 298 patients.
† Overlapping categories.
DSS = discrete subaortic stenosis; LVOT = left ventricular outflow tract obstruction.
Figure Legends:

**Figure 1.** Kaplan-Meier plots. (A) Survival and intervention-free survival for DSS patients and expected survival for the normal age-matched Dutch population. (B) By gender. *DSS = discrete subaortic stenosis*

**Figure 2.** Discrete subaortic stenosis over time. Evolution of discrete subaortic stenosis over time postoperatively by age at time of diagnosis (p=0.048) and gender (p=0.059).

**Figure 3.** Aortic regurgitation over time. Probability of postoperative aortic regurgitation over time.

**Figure 4.** Pre-operative LVOT gradient versus postoperative aortic regurgitation. Association between various levels of pre-operative peak LVOT gradient and probability of postoperative aortic regurgitation progression over time. *LVOT = left ventricular outflow tract.*
Figure 1
Figure 2
Figure 3

Probability of Aortic Regurgitation vs. Time post-operatively (years)

- none
- grade 1
- grade 2
- grade 3

p = 0.764
Figure 4
Surgical Outcome of Discrete Subaortic Stenosis in Adults: A Multicenter Study

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**SUPPLEMENTAL MATERIAL**

In this online supplement, coefficients with standard errors and p-values are provided for the covariates in the mixed-effects model.

**Main effect** = effect of a covariate on the outcome at baseline (intercept).

**Interaction effect** = effect of a covariate on the outcome in time (slope).

For the Cox regression models the hazard ratios and p-values are provided for each covariate.
**Supplemental Table 1. Hazard ratios from Cox regression models for intervention-free survival.**

<table>
<thead>
<tr>
<th>Covariates</th>
<th>Hazard ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(95% confidence interval)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cox model with baseline covariates</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Pre-operative peak instantaneous LVOT gradient ≥80 mmHg</td>
<td>1.016 (1.004 – 1.028)</td>
<td>0.011 *</td>
</tr>
<tr>
<td></td>
<td>1.021 (1.007 – 1.035)</td>
<td>0.002 *</td>
</tr>
<tr>
<td>- Difference between pre- and post-operative LVOT gradient (Delta)</td>
<td>1.022 (0.658 – 1.589)</td>
<td>0.921</td>
</tr>
<tr>
<td>- Type of surgery (enucleation +/- myectomy)</td>
<td>1.003 (0.980 – 1.027)</td>
<td>0.793</td>
</tr>
<tr>
<td>- Age at time of surgery</td>
<td>1.012 (0.977 – 1.048)</td>
<td>0.507</td>
</tr>
<tr>
<td>- Age at time of diagnosis</td>
<td>1.689 (0.752 – 3.794)</td>
<td>0.205</td>
</tr>
<tr>
<td>- Gender (female)</td>
<td>1.531 (1.018 – 2.302)</td>
<td>0.040 *</td>
</tr>
<tr>
<td>- History of prior intracardiac surgery</td>
<td>1.368 (0.901 – 2.076)</td>
<td>0.143</td>
</tr>
<tr>
<td>- Presence of associated CHD</td>
<td>1.095 (0.861 – 1.394)</td>
<td>0.459</td>
</tr>
<tr>
<td>- Smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Joint model (with longitudinal LVOT gradient model)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Age at time of surgery</td>
<td>1.046 (1.044 – 1.048)</td>
<td>&lt;0.001 *</td>
</tr>
<tr>
<td>- Gender (female)</td>
<td>1.387 (0.840 – 2.290)</td>
<td>0.202</td>
</tr>
<tr>
<td>- Peak LVOT gradient progression over time</td>
<td>1.454 (1.308 – 1.616)</td>
<td>&lt;0.001 *</td>
</tr>
<tr>
<td><strong>Time-dependent Cox model (for AR over time)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Age at time of surgery</td>
<td>1.006 (0.987 – 1.025)</td>
<td>0.552</td>
</tr>
<tr>
<td>- Gender (female)</td>
<td>1.493 (0.999 – 1.967)</td>
<td>0.097</td>
</tr>
<tr>
<td>- Aortic regurgitation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>o Mild AR</td>
<td>0.640 (0.050 – 1.330)</td>
<td>0.205</td>
</tr>
<tr>
<td>o Moderate AR</td>
<td>0.783 (0.121 – 1.445)</td>
<td>0.469</td>
</tr>
<tr>
<td>o Severe AR</td>
<td>1.441 (0.782 – 2.099)</td>
<td>0.277</td>
</tr>
</tbody>
</table>

AR = aortic regurgitation; LVOT = left ventricular outflow tract; CHD = congenital heart disease.

* p<0.05.
Supplemental Table 2. LVOT gradient: estimated coefficients, standard errors and p-values from the linear mixed-effects model. To take into account that peak LVOT gradient values exhibited a slightly skewed shape of distribution, a square root transformation was applied.

<table>
<thead>
<tr>
<th>Covariates</th>
<th>Coefficient</th>
<th>Standard error</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Intercept)</td>
<td>3.768</td>
<td>0.378</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time</td>
<td>0.136</td>
<td>0.042</td>
<td>0.001 *</td>
</tr>
</tbody>
</table>

**Main effect**

- Pre-operative peak instantaneous LVOT gradient 0.082 0.008 <0.001 *
- Difference between pre- and post-operative LVOT gradient (Delta) -0.082 0.008 <0.001 *
- Type of surgery (enucleation +/- myectomy) -0.143 0.193 0.458
- Age at time of surgery -0.030 0.009 0.001 *
- Age at time of diagnosis 0.015 0.011 0.183
- Gender (male) -0.487 0.190 0.010 *
- Presence of associated CHD -0.053 0.185 0.774
- Former smoking -0.241 0.352 0.494
- Current smoking -0.122 0.230 0.597

**Interaction effect**

- Pre-operative peak instantaneous LVOT gradient 0.000 0.001 0.738
- Difference between pre- and post-operative LVOT gradient (Delta) 0.000 0.001 0.532
- Type of surgery (enucleation +/- myectomy) -0.004 0.020 0.845
- Age at time of surgery -0.001 0.001 0.205
- Age at time of diagnosis 0.003 0.002 0.048 *
- Gender (male) -0.037 0.019 0.059 *
- Presence of associated CHD -0.030 0.019 0.118
- Former smoking 0.012 0.035 0.736
- Current smoking 0.029 0.024 0.235

LVOT = left ventricular outflow tract; CHD = congenital heart disease. * p<0.05.
**Supplemental Table 3. Aortic regurgitation: estimated coefficients, standard errors and p-values from the continuation ratio mixed-effects model.**

<table>
<thead>
<tr>
<th>Covariates</th>
<th>Coefficient</th>
<th>Standard error</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Intercept)</td>
<td>0.389</td>
<td>1.081</td>
<td>0.719</td>
</tr>
<tr>
<td>Time</td>
<td>0.027</td>
<td>0.090</td>
<td>0.764</td>
</tr>
</tbody>
</table>

**Main effect**

- Pre-operative peak instantaneous LVOT gradient  
  -0.050  
  Standard error: 0.019  
  p-value: 0.008 *

- Difference between pre- and post-operative LVOT  
  gradient (Delta)  
  0.029  
  Standard error: 0.019  
  p-value: 0.138

- Type of surgery (enucleation +/- myectomy)  
  -0.272  
  Standard error: 0.467  
  p-value: 0.560

- Age at time of surgery  
  0.023  
  Standard error: 0.023  
  p-value: 0.326

- Age at time of diagnosis  
  -0.002  
  Standard error: 0.027  
  p-value: 0.934

- Gender (male)  
  -0.241  
  Standard error: 0.465  
  p-value: 0.605

- Presence of associated CHD  
  1.018  
  Standard error: 0.527  
  p-value: 0.053

- Former smoking  
  0.607  
  Standard error: 0.860  
  p-value: 0.480

- Current smoking  
  -0.100  
  Standard error: 0.555  
  p-value: 0.858

**Interaction effect**

- Pre-operative peak instantaneous LVOT gradient  
  -0.004  
  Standard error: 0.002  
  p-value: 0.008 *

- Difference between pre- and post-operative LVOT  
  gradient (Delta)  
  0.003  
  Standard error: 0.002  
  p-value: 0.112

- Type of surgery (enucleation +/- myectomy)  
  -0.070  
  Standard error: 0.038  
  p-value: 0.064

- Age at time of surgery  
  -0.004  
  Standard error: 0.002  
  p-value: 0.066

- Age at time of diagnosis  
  0.002  
  Standard error: 0.003  
  p-value: 0.434

- Gender (male)  
  -0.004  
  Standard error: 0.036  
  p-value: 0.914

- Presence of associated CHD  
  -0.082  
  Standard error: 0.042  
  p-value: 0.051

- Former smoking  
  -0.052  
  Standard error: 0.059  
  p-value: 0.378

- Current smoking  
  0.038  
  Standard error: 0.043  
  p-value: 0.377

LVOT = left ventricular outflow tract; CHD = congenital heart disease. * p<0.05.