Natural history of discrete subaortic stenosis in adults: a multicentre study

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Aims

Discrete subaortic stenosis (DSS) is often diagnosed early in life and known for its sometimes rapid haemodynamic progression in childhood with strong association with aortic regurgitation (AR). However, data about the evolution of DSS in adulthood are scarce. Therefore, we aimed to evaluate the natural history of DSS, and identify risk factors for the progression of DSS, AR, and intervention-free survival.

Methods and results

Conservatively managed adult DSS patients were included in this retrospective multicentre cohort study. Mixed-effects and joint models were used to assess the progression of DSS and AR, and intervention-free survival. Longitudinal natural history data were available for 149 patients [age 20 (IQR: 18–34) years, 48% male]. Sixty patients (40.3%) had associated congenital heart defects (CHDs). The median follow-up duration was 6.3 (IQR: 3.0–12.4) years. The baseline peak left ventricular outflow tract (LVOT) gradient was 32.3 ± 17.0 mmHg and increased by 0.8 ± 0.1 mmHg/year. While the baseline LVOT gradient (P = 0.891) or age (P = 0.421) did not influence the progression rate, the presence of associated CHD was associated with faster progression (P = 0.005). Mild AR was common (58%), but did not significantly progress over time (P = 0.701). The median intervention-free survival was 16 years and associated with the baseline LVOT gradient [hazard ratio (HR) = 3.9 (95% CI: 2.0–7.6)], DSS progression [HR = 2.6 (95% CI: 2.0–3.5)], and AR [HR = 6.4 (95% CI 2.6–15.6)].

Conclusion

In contrast to children, DSS progresses slowly in adulthood. In particular, patients with associated CHD are at risk for faster progression and should be monitored cautiously. Discrete subaortic stenosis progression is not influenced by the baseline LVOT gradient or age. Mild AR is common, but non-progressive over time.

Keywords

Subaortic stenosis • Natural history • Congenital heart defects • Aortic regurgitation

Introduction

Fibromuscular discrete subaortic stenosis (DSS) is often diagnosed early in life and notable for its unpredictable, but sometimes rapid haemodynamic progression during childhood.1–4 Aortic regurgitation (AR) is present in 30–80% of patients and thought to develop secondary to aortic valve damage caused by the high-velocity subvalvular jet.1–11 In children, the natural history is well established and several predictors for haemodynamic progression have been identified such as younger age or a higher gradient at diagnosis.1,12–14 Despite the fact that DSS is a relatively frequent abnormality (6.5%) in adults with congenital heart defects (CHD), data about DSS in adulthood are scarce.5,8,15–16 In contrast to infants and children, adults with DSS seem to have a slower progression rate.7 However, there is a lack in studies focusing on the elucidation of factors that predict DSS or AR progression in adults. Therefore, the main purpose of this study was to evaluate the natural
history of DSS in a large cohort of adults and identify risk factors for DSS progression, AR progression, and the need for surgery.

Methods

All adult patients (18 years or older) with a pre-existing diagnosis of fibromuscular DSS seen between January 1980 and October 2011 at the Congenital Cardiac Centre for Adults of one of the participating centres (Erasmus University Medical Centre, Rotterdam, The Netherlands; University Hospital Gasthuisberg, Leuven, Belgium; Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands; Toronto Congenital Cardiac Centre for Adults located at Peter Munk Cardiac Centre, Toronto, Canada) were evaluated for eligibility. Fibromuscular DSS was defined as ‘encirclement of the left ventricular outflow tract (LVOT) by a membrane or short-segment stenosis consisting of fibrous or fibromuscular tissue’. Eligible patients were selected from the CONCOR database,19 the Dutch registry for adult patients with CHD, and the Leuven and Toronto database for adults with CHD.

Exclusion criteria were: prior surgical resection of subaortic tissue, lack of serial echocardiographic examinations, predominant dynamic subaortic obstruction due to hypertrophic cardiomyopathy, subvalvular obstruction caused by accessory mitral valve tissue or the support system of mitral valve prosthesis, complex LVOT obstruction (tunnel-like subaortic narrowing), concomitant moderate-to-severe valvular aortic stenosis, transposition of the great arteries, or univentricular connections. This retrospective study was approved by the institutional review board and ethical committee of the participating centres. 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. Baseline was defined as entry into the study (first available echocardiogram in adulthood). Follow-up was defined as the time between the first and last available echocardiogram. Peak systolic instantaneous LVOT gradient was derived from the continuous wave Doppler LVOT peak flow velocity from the apical three- or five-chamber views. The degree of AR was graded by experienced echocardiographers and cardiologists as mild, moderate, or severe.20 The left ventricular (LV) mass was calculated using the modified Devereux formula.21 The aorto-septal angle was measured in the parasternal long-axis view at end-diastole, as previously described.22

Statistical analysis

The Statistical Package for Social Sciences, version 19.0 (SPSS, Inc., Chicago, IL, USA) was used for descriptive data analysis. Normally distributed continuous variables were summarized using the mean ± standard deviation (SD). Non-normally distributed continuous variables were summarized using the median and the inter-quartile range (IQR). Categorical variables were summarized using the frequency and percentage. Group differences in baseline variables were assessed using the two-sample t-test, the χ² test, or the Mann–Whitney U test. All statistical tests were two-sided; a P-value < 0.05 was considered statistically 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 model analyses were used. In particular, for the LVOT gradient progression rate a linear mixed-effects model was used, whereas for AR progression a mixed-effects continuation ratio model was employed.24 The following factors were included in the models as covariates: age at baseline, age at diagnosis, gender, prior intracardiac surgery, additional CHDs, baseline LVOT gradient (< or ≥ 50 mmHg), aortic valve morphology, LV mass, ventricular septal defect (VSD), AR, aorto-septal angle, 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. Wald tests were used to assess which prognostic factors were most associated with the progression of the LVOT gradient and AR.

Probabilities of intervention-free survival from baseline were obtained by the Kaplan–Meier method. Survival of DSS patients was compared with the expected survival of the normal Dutch population.25 Patients were censored at the 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 with the number of covariates. A joint modelling approach and time-dependent Cox model were respectively used to investigate the effect of the LVOT gradient and AR on the hazard ratio (HR).26

Results

Out of 427 identified patients with fibromuscular DSS, longitudinal natural history data were available for 149 patients (Figure 1). Baseline characteristics are summarized in Table 1. Sixty patients (40.3%) had associated CHD (Table 1). The median follow-up duration was 6.3 (IQR: 3.0–12.4) years, yielding a total of 1191 patient-years. On average 2.7 ± 0.9 (range 2–9) echocardiographic studies were available for each patient.

Progression of left ventricular outflow tract gradient over time

The peak systolic instantaneous LVOT gradient was 32.3 ± 17.0 mmHg at baseline and linearly increased over time with a rate of 0.8 ± 0.1 mmHg per year. Six patients demonstrated a progression rate >5 mmHg/year. The presence of an associated CHD was associated with faster progression of the LVOT gradient (P = 0.005; Figure 2); in particular a VSD (P = 0.035). The LVOT gradient progression rate was not influenced by the age at baseline (P = 0.421), age at time of diagnosis (P = 0.273), gender (P = 0.960), prior intracardiac surgery (P = 0.162), baseline LVOT gradient ≥ 50 mmHg (P = 0.891; Figure 2), current smoking (P = 0.282), or aortic valve morphology (P = 0.240) (see Supplementary material online, Table S1).

Progression of aortic regurgitation over time

A LVOT gradient ≥ 50 mmHg (P = 0.007) was independently associated with a higher probability of having AR (see Supplementary material online Table S2). Although Figure 3 demonstrates that over a period of 10 years the probability of not having AR decreases from...
~40 to ~20%, progression to moderate-to-severe AR was rare. Overall, the AR severity did not significantly progress over time \((P = 0.747)\). A baseline peak LVOT gradient \(\geq 50\) mmHg did not influence the progression of AR \((P = 0.999)\). There were no factors significantly associated with progression from mild to moderate-to-severe AR (see Supplementary material online, Table S2).

**Clinical outcome**

Two patients died suddenly 4 and 16 years after entry in the study (37 and 39 years old, LVOT gradients before death 63 and 85 mmHg, respectively, no associated CHD, no left ventricular hypertrophy). The cause of death was unknown in both patients (no autopsy). The cumulative survival was 94% at 20 years (0.17% per patient-year; Figure 4A). One patient was successfully resuscitated after an episode of ventricular fibrillation (36 years old, LVOT gradient before the event 49 mmHg, associated repaired VSD and left ventricular hypertrophy). Two patients (22-year-old male and 52-year-old female, LVOT gradients 21 and 64 mmHg, respectively, both had an associated unrepaired VSD and mild AR) had an episode of endocarditis (0.17% per patient-year).

During follow-up 41 patients required surgery for DSS according to the clinical practice guidelines (5.9% per patient-year). The median intervention-free survival was 16 years (Figure 4A). The mean age at the time of DSS surgery was 35.1 ± 14.0 years. The pre-operative LVOT gradient was 75.3 ± 3.6 mmHg and 17 of the 41 patients (41.5%) had moderate-to-severe AR. The type of DSS surgery was enucleation in 20 patients (48.8%) and enucleation with additional myectomy in 21 patients (51.2%). Nineteen patients (46.3%) underwent concomitant surgery: aortic valve replacement (n = 16) or VSD closure (n = 3). Post-operative complications included bleeding requiring rethoracotomy (n = 1), atrial fibrillation (n = 4), complete AV block requiring permanent pacemaker implantation (n = 3), and heart failure (n = 1).

Independent predictors for impaired intervention-free survival were the baseline LVOT gradient \(\geq 50\) mmHg [HR: 3.9 (95% CI: 2.0–7.6); Figure 4B], LVOT gradient progression over time [HR 2.6 (95% CI: 2.0–3.5)], and moderate-to-severe AR [HR 6.4 (95% CI: 2.6–15.6)] (see Supplementary material online, Table S3).

**Discussion**

This study is the first large longitudinal study focusing on the natural course of DSS over time and risk factors influencing the
Table 1  Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Discrete subaortic stenosis patients (n = 149)</th>
<th>Intervention-free survival group (n = 106)</th>
<th>Patients with an event (surgery or death) (n = 43)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>72 (48.3)</td>
<td>52 (49.1)</td>
<td>20 (46.5)</td>
<td>0.778</td>
</tr>
<tr>
<td>Age at baseline, years</td>
<td>20.4 (17.6–33.8)</td>
<td>20.2 (17.5–33.6)</td>
<td>20.5 (17.8–34.2)</td>
<td>0.701</td>
</tr>
<tr>
<td>Age at DSS diagnosis, years</td>
<td>17.0 (7.5–30.5)</td>
<td>18.8 (7.4–31.8)</td>
<td>16.7 (5.9–29.0)</td>
<td>0.81</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25.4 ± 5.5</td>
<td>25.8 ± 6.1</td>
<td>24.6 ± 3.9</td>
<td>0.251</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>125.6 ± 16.6</td>
<td>125.9 ± 16.6</td>
<td>125.1 ± 16.6</td>
<td>0.787</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>74.9 ± 10.3</td>
<td>75.5 ± 10.2</td>
<td>73.5 ± 10.6</td>
<td>0.282</td>
</tr>
<tr>
<td>Peak systolic instantaneous LVOT gradient, mmHg</td>
<td>32.3 ± 17.0</td>
<td>28.4 ± 14.1</td>
<td>41.9 ± 19.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≤30 mmHg</td>
<td>76 (51.0)</td>
<td>64 (60.4)</td>
<td>12 (27.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>30–50 mmHg</td>
<td>51 (34.2)</td>
<td>33 (31.1)</td>
<td>18 (41.9)</td>
<td></td>
</tr>
<tr>
<td>≥50 mmHg</td>
<td>22 (14.8)</td>
<td>9 (8.5)</td>
<td>13 (30.2)</td>
<td></td>
</tr>
<tr>
<td>Aortic regurgitation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None/trivial</td>
<td>57 (38.3)</td>
<td>44 (41.5)</td>
<td>13 (30.2)</td>
<td>0.085</td>
</tr>
<tr>
<td>Mild</td>
<td>86 (57.8)</td>
<td>61 (57.5)</td>
<td>25 (58.1)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>5 (3.4)</td>
<td>1 (9.4)</td>
<td>4 (9.3)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>1 (0.7)</td>
<td>0 (0.0)</td>
<td>1 (2.3)</td>
<td></td>
</tr>
<tr>
<td>Associated CHD/repaired</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>89 (59.7)</td>
<td>63 (59.4)</td>
<td>26 (60.5)</td>
<td>0.961</td>
</tr>
<tr>
<td>Ventricular septal defect</td>
<td>24 (16.1)/7 (4.7)</td>
<td>17 (16.0)/5 (4.7)</td>
<td>7 (16.3)/2 (4.7)</td>
<td>0.971</td>
</tr>
<tr>
<td>Atrial septal defect</td>
<td>11 (7.4)/6 (4.0)</td>
<td>9 (8.5)/5 (4.7)</td>
<td>2 (4.7)/1 (2.3)</td>
<td>0.417</td>
</tr>
<tr>
<td>Valvular aortic stenosis (&lt;3 m/s)</td>
<td>7 (4.7)/0 (0.0)</td>
<td>2 (1.9)/0 (0.0)</td>
<td>5 (11.6)/0 (0.0)</td>
<td>0.011</td>
</tr>
<tr>
<td>Coarctation of the aorta</td>
<td>15 (10.1)/6 (4.0)</td>
<td>10 (9.4)/4 (3.8)</td>
<td>5 (11.6)/2 (4.7)</td>
<td>0.687</td>
</tr>
<tr>
<td>Persistent ductus arteriosus</td>
<td>6 (4.0)/4 (2.7)</td>
<td>4 (3.8)/3 (2.8)</td>
<td>2 (4.7)/1 (2.3)</td>
<td>0.805</td>
</tr>
<tr>
<td>Shone’s complex</td>
<td>2 (1.3)/0 (0.0)</td>
<td>0 (0.0)/0 (0.0)</td>
<td>2 (4.7)/0 (0.0)</td>
<td>0.025</td>
</tr>
<tr>
<td>Aortic-septal angle, a-b</td>
<td>138.2 ± 16.2</td>
<td>138.8 ± 16.8</td>
<td>133.6 ± 11.0</td>
<td>0.423</td>
</tr>
<tr>
<td>Left atrial diameter, mm</td>
<td>36.6 ± 8.4</td>
<td>35.9 ± 7.7</td>
<td>40.1 ± 10.8</td>
<td>0.058</td>
</tr>
<tr>
<td>Indexed for BSA, mm/m²</td>
<td>20.1 ± 5.2</td>
<td>19.5 ± 4.8</td>
<td>22.6 ± 6.4</td>
<td>0.028</td>
</tr>
<tr>
<td>LV mass, g</td>
<td>174.0 ± 65.0</td>
<td>164.9 ± 55.8</td>
<td>215.6 ± 86.8</td>
<td>0.003</td>
</tr>
<tr>
<td>Indexed for BSA, g/m²</td>
<td>94.6 ± 35.1</td>
<td>88.6 ± 27.9</td>
<td>121.5 ± 49.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVOT diameter, mm</td>
<td>16.5 ± 3.3</td>
<td>16.4 ± 3.4</td>
<td>17.0 ± 3.0</td>
<td>0.64</td>
</tr>
<tr>
<td>LV end-diastolic diameter, mm (IQR)</td>
<td>46.8 ± 6.7 (41.0–51.0)</td>
<td>46.1 ± 6.2 (40.0–50.0)</td>
<td>50.1 ± 8.0 (46.5–56.3)</td>
<td>0.059</td>
</tr>
<tr>
<td>Indexed for BSA, mm/m²</td>
<td>25.8 ± 4.3</td>
<td>25.2 ± 3.9</td>
<td>28.4 ± 5.3</td>
<td>0.004</td>
</tr>
<tr>
<td>LV end-systolic diameter, mm (IQR)</td>
<td>28.3 ± 5.6 (25.0–32.0)</td>
<td>27.8 ± 5.3 (24.3–31.0)</td>
<td>30.6 ± 6.8 (24.8–35.0)</td>
<td>0.053</td>
</tr>
<tr>
<td>Indexed for BSA, mm/m²</td>
<td>15.6 ± 3.5</td>
<td>15.2 ± 3.1</td>
<td>17.4 ± 4.6</td>
<td>0.013</td>
</tr>
<tr>
<td>Fractional shortening, %</td>
<td>39.7 ± 7.2</td>
<td>39.8 ± 7.1</td>
<td>38.9 ± 7.9</td>
<td>0.641</td>
</tr>
<tr>
<td>Maximum exercise capacity, % from norm</td>
<td>86.3 ± 22.3</td>
<td>86.6 ± 21.8</td>
<td>85.8 ± 23.4</td>
<td>0.256</td>
</tr>
<tr>
<td>Sinus rhythm</td>
<td>146 (98.0)</td>
<td>104 (98.1)</td>
<td>42 (97.7)</td>
<td>0.283</td>
</tr>
<tr>
<td>Heart frequency, b.p.m.</td>
<td>71.9 ± 14.5</td>
<td>72.5 ± 14.6</td>
<td>70.3 ± 14.5</td>
<td>0.487</td>
</tr>
<tr>
<td>QRS duration, ms</td>
<td>101.8 ± 20.8</td>
<td>98.7 ± 17.5</td>
<td>110.8 ± 26.6</td>
<td>0.005</td>
</tr>
<tr>
<td>PR time, ms</td>
<td>154.6 ± 34.3</td>
<td>153.6 ± 35.8</td>
<td>157.0 ± 30.3</td>
<td>0.64</td>
</tr>
<tr>
<td>NYHA class I</td>
<td>144 (96.6)</td>
<td>104 (98.1)</td>
<td>40 (93.0)</td>
<td>0.118</td>
</tr>
</tbody>
</table>

Continued
clinical outcome in adult patients. Given the scarcity of data about the natural evolution of DSS in adults, these results will contribute to our understanding of the clinical course of DSS in adulthood and guide clinical management.

Progression of discrete subaortic stenosis

Interestingly, the present study demonstrates that DSS in adulthood progresses very slowly, with <1 mmHg gradient increase per year. These results confirm the findings of a series published by Oliver et al.\(^7\) that showed a similar slow progression rate in only 25 patients with sequential echocardiographic studies. Remarkably, the slow progression rate along several decades in adults contrasts to the progressive nature of DSS described in children.\(^1^{–}4\) This phenomenon might be explained by the fact that

<table>
<thead>
<tr>
<th>Smoking</th>
<th>Discrete subaortic stenosis patients (n = 149)</th>
<th>Intervention-free survival group (n = 106)</th>
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<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>112 (75.2)</td>
<td>84 (79.2)</td>
<td>28 (65.1)</td>
<td>0.323</td>
</tr>
<tr>
<td>Former</td>
<td>11 (7.4)</td>
<td>6 (5.7)</td>
<td>5 (11.6)</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>26 (17.4)</td>
<td>16 (15.1)</td>
<td>10 (23.3)</td>
<td></td>
</tr>
</tbody>
</table>

Values are expressed as n (%), median (IQR), or mean ± SD.
BSA, body surface area; CHD, congenital heart defects; DSS, discrete subaortic stenosis; IQR, inter-quartile range; LV, left ventricular; LVOT, left ventricular outflow tract; NYHA, New York Heart Association.

\(^a\)Diagnoses are not mutually exclusive (one patient could have multiple associated CHDs).

\(^b\)This variable was only available for 82 patients.

![Table 1](https://academic.oup.com/eurheartj/article-abstract/34/21/1548/466516/1552)

![Figure 2](https://academic.oup.com/eurheartj/article-abstract/34/21/1548/466516/1552)

The study by Oliver et al.\(^7\) suggested that age influences DSS evolution, since they found significant correlations between age and LVOT gradient and progression. To evaluate if age was not only correlated but could actually significantly predict DSS disease progression, we explored age as a covariate in longitudinal echocardiographic models in this large population. However, neither age at the study baseline nor age at the time of diagnosis significantly influenced LVOT progression over time. Furthermore, in contrast to paediatric populations, we did not find an association between DSS severity at baseline and the progression rate in adults who naturally survived into adulthood.\(^1\)\(^,\)\(^12\)\(^–\)\(^14\) Thus, patients with
LVOT gradients $\geq$ 50 mmHg were not at risk for faster progression of the LVOT obstruction.

With respect to the prevalence of associated CHD, our population was comparable with those described in other studies. Notably, the presence of an associated CHD, particularly a VSD, was the only independent predictor for DSS progression. Many previous studies have tried to elucidate the poorly understood aetiology of DSS. It has been demonstrated that abnormal geometric arrangements in the LVOT, such as steepened aorto-septal angle, malaligned VSD, and mitral-aortic separation, may induce increased shear stress. Cellular flow studies have shown that increased shear stress triggers growth factors and cellular proliferation, eventually stimulating development of the subaortic membrane and progression of the LVOT obstruction. Our findings suggest that adult DSS patients with associated CHD and those without additional CHD compile two different subgroups within the DSS spectrum. We hypothesize that the presence of associated CHD, particularly a VSD, causes more abnormal haemodynamic forces at the LVOT level, which could be caused either by the CHD itself or by prior intracardiac surgery for that defect. The abnormal haemodynamic forces might cause increased shear stress, thereby evoking a more intense response on a cellular level and faster progression of the LVOT obstruction. We tried to elucidate whether the aorto-septal angle influenced LVOT progression over time, but unfortunately there were too many missing values for this covariate. Future rheological studies in adult DSS patients are certainly warranted to test this hypothesis.

Aortic regurgitation

The most commonly described haemodynamic sequel in DSS patients is AR, which is thought to evolve secondary to the high-velocity subvalvular jet produced by the LVOT obstruction. In an attempt to prevent damage to the aortic valve, early surgical resection of the subaortic membrane has been advocated. However, Oliver et al. demonstrated in 25 adults that AR is common, and usually mild, and non-progressive over time. Similarly, our study clearly showed that AR is only haemodynamically relevant (moderate-to-severe) in a minority of patients although mild AR is found in the majority of adult DSS patients. More importantly, while $\sim$20% of patients developed mild AR during the study period, progression to moderate-to-severe is rare. In the total group, the AR progression was not statistically significant and we could not identify a subgroup of patients at a higher risk for progression. Therefore, the fear of development of progressive AR seems to be overestimated and early surgical repair of DSS in adult patients with a low LVOT gradient and no/mild AR is not justified.

Survival

Overall, the cumulative 20-year survival of patients with DSS is comparable with the survival of the age-matched normal Dutch population. Since the life expectancy of Canada, the Netherlands and Belgium is comparable, this probably does not influence our survival results at a young adult age. However, the rate of (near) sudden death (0.17–0.25% per patient-year) in our study of young adult patients with DSS is worrisome. This seems to be higher than the generally estimated 0.09% per patient-year in adult patients with any type of CHD. Moreover, it represents a 30–125 times increased risk of sudden death compared with the general population with a similar age range. Unfortunately, the absolute number of events was too small to identify any risk factors for sudden death in patients with DSS.

Clinical implications

Discrete subaortic stenosis progresses very slowly in adulthood; however, patients with associated congenital lesions, particularly a VSD, are at risk for faster disease progression and should be monitored cautiously. Furthermore, this large study shows that AR is usually mild and does not progress over time, thereby rejecting the hypothesis that early repair is required to prevent development of progressive AR.

According to the present study, prophylactic surgery in asymptomatic adult DSS patients is not indicated solely to prevent rapid progression of the LVOT obstruction or progressive AR. Our data do not support the current North American guidelines that state...
that surgical intervention should be recommended in any DSS patient with a peak LVOT gradient ≥ 50 mmHg, but are more in line with the European and Canadian guidelines. However, the timing of surgical intervention is a highly complex issue compiling various factors in an individual patient-based approach: the peak LVOT gradient, progression rate of the LVOT gradient, severity and progression of AR, presence of associated CHD, LV diameter and function, and risk of sudden death. Postponing surgery to higher LVOT gradients might increase the chance of requirement of concomitant aortic valve repair or replacement and increase the risk of sudden death. On the other hand, until now it is unclear whether surgery will prevent or at least minimize the risk of sudden death. Unfortunately, the optimal timing of surgical intervention in adult patients with DSS cannot yet be derived from the present study.

Since endocarditis only occurred in two patients with a concomitant unrepaired VSD, it is likely that these cases were related to the unrepaired VSD rather than DSS. Thus, the risk of

Figure 4 Kaplan–Meier plots. (A) Cumulative Kaplan–Meier survival and intervention-free survival for discrete subaortic stenosis patients and expected survival for the normal Dutch population. (B) Cumulative Kaplan–Meier intervention-free survival for discrete subaortic stenosis patients with a baseline peak systolic instantaneous left ventricular outflow tract gradient < 50 mmHg compared with ≥ 50 mmHg (P < 0.001). DSS, discrete subaortic stenosis; LVOT, left ventricular outflow tract.
endocarditis in patients with isolated DSS seems to be low and endocarditis prophylaxis should only be indicated in high-risk patients.44 Since the LVOT gradient progression is generally slow and AR is usually mild, echocardiographic follow-up can probably be limited to 3–5-year intervals for the majority of patients. However, for patients with associated congenital lesions (particularly a VSD), peak LVOT gradient ≥50 mmHg, or moderate-to-severe AR, more frequent echocardiographic follow-up evaluations seem reasonable, for example, every 1–2 years.

Study limitations
This retrospective study inheriting all limitations of a retrospective study design included patients monitored in adult congenital clinics at tertiary care centres, and therefore a referral bias may exist. Inclusion of deceased patients from the databases limited 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. Finally, we have to acknowledge that the median follow-up duration of 6.3 years was relatively short. For definitive conclusions regarding the long-term outcome of DSS in adulthood, a longer follow-up period is required.

Conclusions
Conservatively (non-surgically) managed DSS progresses slowly in adulthood, though patients with associated congenital lesions, especially a VSD, are at risk for faster DSS progression and should be monitored cautiously. The baseline LVOT gradient does not influence DSS progression over time, and thus should not be used as the sole indication to proceed to surgery. AR is usually mild and does not progress over time, indicating that prophylactic surgery to prevent AR progression is not justified.

Supplementary material
Supplementary material is available at European Heart Journal online.

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