

# Influence of Atypical Symptoms and Electrocardiographic Signs of Left Ventricular Hypertrophy or ST-Segment/T-Wave Abnormalities on the Natural History of Otherwise Asymptomatic Adults with Moderate to Severe Aortic Stenosis: Preliminary Communication

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**Background and aim of the study:** Current guidelines recommend that aortic valve replacement (AVR) is deferred in asymptomatic patients with aortic stenosis until symptoms develop. Classical symptoms include exertional dyspnea, angina pectoris and syncope. The influence of atypical symptoms (dizziness, exertional intolerance, fatigue, palpitations/arrhythmias) and electrocardiographic signs of left ventricular hypertrophy or ST-segment/T-wave abnormalities on the natural course of the disease is unknown.

**Methods:** The clinical course of 100 patients with a preliminary diagnosis of asymptomatic aortic stenosis with respect to clinical signs and symptoms mentioned above was examined. All patients underwent serial echocardiographic examinations with calculation of aortic valve area by the continuity equation.

**Results:** Two patients died during a mean follow up period of  $34 \pm 32$  months (range: 1-116 months). There were no peri- or postoperative deaths. Seven patients with hemodynamically severe aortic stenosis and concomitant atrial fibrillation, four with classical symptoms after re-evaluation, and five with left ventricular dysfunction underwent short-term AVR and

were excluded from any subsequent analysis. In total, 84 patients were either entirely asymptomatic ( $n = 57$ ; group A) or had atypical symptoms ( $n = 27$ ; group B). Of these patients, 18 underwent AVR before onset of classical symptoms for various reasons, and 21 were treated medically. The remaining 15 group B patients exhibited classical symptoms significantly earlier than the remaining 30 group A patients ( $15 \pm 7$  versus  $35 \pm 24$  months;  $p < 0.002$ ). Aortic valve area tended to decrease more rapidly in group B patients than in group A patients ( $-0.16 \pm 0.12$  versus  $-0.11 \pm 0.07$   $\text{cm}^2$  per year;  $p = 0.053$ ). Clinical and hemodynamic progression were further increased if additional electrocardiographic abnormalities were present.

**Conclusion:** Both atypical symptoms and electrocardiographic signs of left ventricular hypertrophy/strain shorten the time interval until otherwise asymptomatic patients exhibit classical symptoms of advanced aortic stenosis requiring prosthetic valve replacement.

The Journal of Heart Valve Disease 2004;13:182-187

The optimal treatment of patients with severe but asymptomatic aortic stenosis is still under debate. Aortic valve replacement (AVR) is recommended in patients with left ventricular dysfunction or an abnormal response to exercise testing (1,2). Surgery is also

advisable if severe valvular calcification, aortic jet velocity  $>4.0$  m/s or an annual increase in aortic jet velocity of  $\geq 0.3$  m/s indicate rapid hemodynamic progression (3-5). With a lower level of evidence, AVR can be considered after manifestation of excessive left ventricular hypertrophy or ventricular arrhythmias (1,2). In the remaining patients, the indication for prosthetic valve replacement is traditionally postponed until clinical symptoms develop (6,7). However, there is no consensus as to which clinical signs or findings classify a patient as 'symptomatic'. In most published studies, classical symptoms of advanced aortic stenosis comprise exertional dyspnea or other signs of congestive heart failure, angina pectoris and syncope (8-14). The

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Presented as a poster at the First Biennial Meeting of the Society for Heart Valve Disease, 15th-18th June 2001, Queen Elizabeth II Conference Centre, London, United Kingdom

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impact of atypical symptoms (dizziness, exertional intolerance, fatigue, palpitations/arrhythmias) and electrocardiographic findings indicative of left ventricular hypertrophy or ischemia on the natural history of aortic valve stenosis has not yet been established. Hence, a pilot study was conducted to address the question of whether the aforementioned parameters increase clinical or hemodynamic progression of aortic stenosis in otherwise asymptomatic individuals.

## Materials and methods

The clinical course of 100 consecutive patients admitted to the authors' institution with the preliminary diagnosis of 'asymptomatic' aortic stenosis (aortic valve area  $\leq 1.5 \text{ cm}^2$ ; mean  $1.0 \pm 0.3 \text{ cm}^2$ ) was assessed prospectively. Clinical data recorded at study entry and during follow up included classical and atypical symptoms (see above for definitions), cardiac rhythm irregularities (complex ventricular arrhythmias  $\geq$

Lown IIIb, new paroxysmal or permanent atrial fibrillation, atrioventricular block, left or right bundle branch block, sinus bradycardia  $< 40 \text{ bpm}$ , or sinus arrest  $> 3 \text{ s}$ ), left ventricular hypertrophy on resting electrocardiogram ( $\text{SV}_1 + \text{RV}_5\text{V}_6 > 3.5 \text{ mV}$ ;  $\text{S}_{\text{max}} + \text{R}_{\text{max}} > 4.5 \text{ mV}$  (precordial leads);  $\text{RI} + \text{S}_{\text{III}} > 2.5 \text{ mV}$ ) and ST-segment-depression  $\geq 0.2 \text{ mV}$  or reversal of T-wave polarity (strain pattern). All patients underwent comprehensive echocardiographic examinations, and aortic valve area was determined using the continuity equation. If left heart catheterization was performed, the Gorlin equation was used for calculation of aortic valve area, and this yielded a close linear correlation with the echocardiographic results. Left ventricular dysfunction was defined as an end-systolic diameter  $> 20 \text{ mm/m}^2$  body surface area and/or fractional shortening  $< 28\%$  in the left parasternal long-axis view. Symptomatic status was graded according to the NYHA classification. Exercise testing was not used to guide therapeutic decision-making in this patient pop-

Table I: Progression of aortic valve stenosis and postoperative functional status in the patient population.

Parameter	Group A (entirely asymptomatic)		Group B (atypical symptoms)	
Initial no. of patients	57		27	
AVR at physician's discretion (n)	1		8	
AVR (atypical symptoms) (n)	4		2	
CABG with concomitant AVR (n)	2		1	
No AVR during follow up (n)	20		1	
Final no. of patients (follow-up until CS)	30		15	
Initial AVA ( $\text{cm}^2$ )*	$1.1 \pm 0.3$		$0.9 \pm 0.2^{1)}$	
Pre-op AVA ( $\text{cm}^2$ )*	$0.7 \pm 0.1$		$0.7 \pm 0.1$	
AVA progression ( $\text{cm}^2/\text{year}$ )*	$-0.11 \pm 0.07$		$-0.16 \pm 0.12$	
Onset of CS (months)*	$35 \pm 24$		$15 \pm 7^{2)}$	
	Group A1 (ECG-)	Group A2 (ECG+)	Group B1 (ECG-)	Group B2 (ECG+)
Final no. of patients (follow up until CS)	23	7	8	7
Initial AVA ( $\text{cm}^2$ )*	$1.1 \pm 0.2$	$0.9 \pm 0.2$	$1.0 \pm 0.2$	$0.8 \pm 0.3^{3)}$
pre-OP AVA ( $\text{cm}^2$ )*	$0.8 \pm 0.2$	$0.7 \pm 0.1$	$0.7 \pm 0.2$	$0.7 \pm 0.1$
AVA progression ( $\text{cm}^2/\text{year}$ )*	$-0.11 \pm 0.08$	$-0.09 \pm 0.04$	$-0.11 \pm 0.07$	$-0.23 \pm 0.15^{4)}$
Onset of CS (months)*	$38 \pm 25^{5)}$	$27 \pm 18^{5)}$	$18 \pm 7^{5)}$	$11 \pm 6^{5)}$
Regular LV function post-op	20	6	5	6
NYHA class I post-op	20	7	5	7

\*Values are mean  $\pm$  SD.

<sup>1)</sup> $p < 0.0001$ ; <sup>2)</sup> $p < 0.002$ ; <sup>3)</sup> $p < 0.05$  versus group A1; <sup>4)</sup> $p < 0.02$  versus group A1;  $p < 0.05$  versus group A2; <sup>5)</sup>For significance level, see Figure 2.

AVA: Aortic valve area; AVR: Aortic valve replacement; CABG: Coronary artery bypass grafting; CS: Classical symptoms; ECG: Electrocardiogram; LV: Left ventricular; post-op: Postoperative; pre-op: Preoperative.

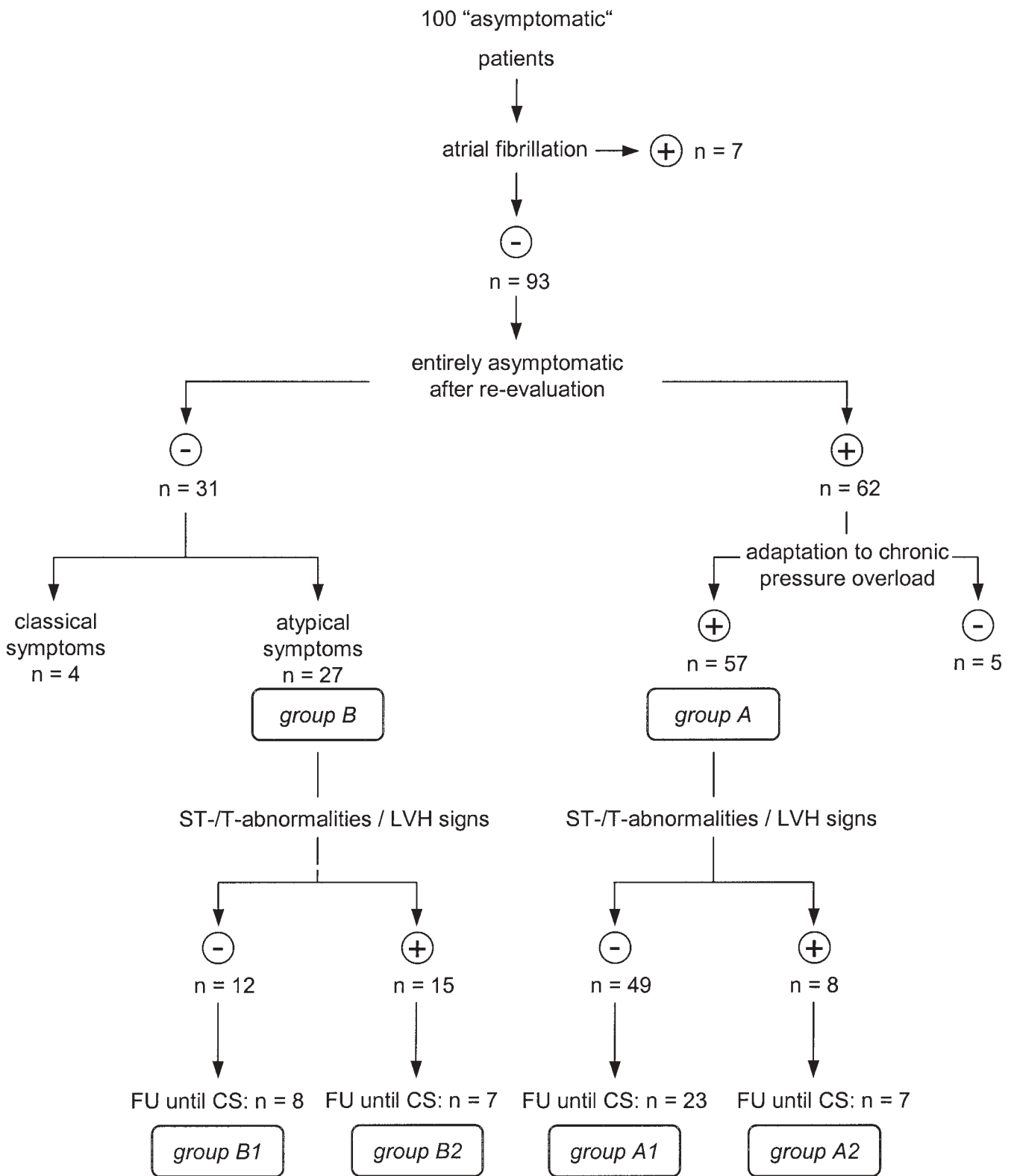


Figure 1: Schematic illustration of the composition of the study population and its subdivision into two groups (A, B) and four subgroups (A1, A2, B1, B2). CS: Classical symptoms; FU: Follow up; LVH: Left ventricular hypertrophy.

ulation. Patients were followed up at three- to six-month intervals at the authors' institution. If patients underwent AVR, a final examination was conducted at five to six months postoperatively.

Data were reported as mean values  $\pm$  SD. Statistical analyses were performed with the unpaired *t*-test for continuous variables and the chi-square test for dichotomous variables. A *p*-value  $<0.05$  was considered to indicate statistical significance.

## Results

During a mean of  $34 \pm 32$  months (range: 1 to 116 months) of follow up, one patient who had refused surgery died suddenly 13 months later. Another patient died from cancer after having remained asymptomatic for 52 months. There were no peri- or postoperative deaths. Seven patients with an aortic valve area of  $0.5\text{--}1.0\text{ cm}^2$  and concomitant atrial fibrillation at study entry, four patients with classical symptoms after re-evaluation, and five with left ventricular dysfunction were excluded from subsequent analysis, as they were advised to undergo urgent valve replacement surgery; this was performed rapidly, except in the patient who refused surgery (Fig. 1). The remaining 84 patients with regular left ventricular function at the time of inclusion were either entirely asymptomatic ( $n = 57$ ; group A) or presented with atypical symptoms ( $n = 27$ ; group B). Seventeen of the 27 group B patients complained of fatigue, eight of exertional intolerance and three of dizziness, and five patients had either palpitations or arrhythmias in the electrocardiogram. Eighteen of the 84 group A and group B patients underwent AVR at the discretion of their attending physicians before onset of classical symptoms ( $n = 9$ ), because of atypical symptoms alone ( $n = 6$ ), or simultaneous with coronary artery bypass sur-

gery ( $n = 3$ ). Twenty-one patients were treated medically (Table I). The remaining 15 group B patients developed classical symptoms significantly earlier than the remaining 30 group A patients ( $15 \pm 7$  versus  $35 \pm 24$  months;  $p < 0.002$ ). There was an insignificant trend towards a more rapid decrease of aortic valve area in group B patients in comparison with group A patients ( $-0.16 \pm 0.12$  versus  $-0.11 \pm 0.07\text{ cm}^2$  per year;  $p = 0.053$ ; Table I). While the initial aortic valve area was significantly smaller in group B patients ( $0.9 \pm 0.2$  versus  $1.1 \pm 0.3\text{ cm}^2$ ;  $p < 0.0001$ ), the preoperative aortic valve area after manifestation of clinical symptoms was similar in both groups.

Group A and group B patients were divided into subgroups without (groups A1 and B1) and with (groups A2 and B2) ST-segment/T-wave-abnormalities or signs of left ventricular hypertrophy in the electrocardiogram (Fig. 1; Table I). If these electrocardiographic abnormalities were present in patients with atypical symptoms (group B2), progression of aortic valve obstruction was much faster than in entirely asymptomatic patients (groups A1 and A2). Moreover, the time interval until development of classical symptoms was significantly shorter than in all other patient subgroups (Fig. 2). Among group A patients, the additional manifestation of ST-segment/T-wave-abnormalities or signs of left ventricular hypertrophy similarly tended to accelerate both clinical and hemodynamic progression, although statistical significance was not achieved. Postoperative left ventricular function and symptomatic status were not significantly different between the four subgroups.

Left ventricular function remained normal during a mean follow up period of  $75 \pm 25$  months (range: 37 to 116 months) in the 21 patients who were not operated on during the study period, and 20 of them were also free from both atypical symptoms and abnormalities in the resting electrocardiogram. In comparison with all of the 29/49 subgroup A1 patients who underwent valve replacement surgery for various indications, the initial aortic valve area was higher ( $1.4 \pm 0.2$  versus  $1.1 \pm 0.3\text{ cm}^2$ ;  $p = \text{NS}$ ) and the decrease in aortic valve area during follow up was less pronounced ( $-0.04 \pm 0.02$  versus  $-0.11 \pm 0.08\text{ cm}^2$  per year;  $p < 0.0005$ ).

## Discussion

The results of this observational study demonstrated that an unselected population of patients with 'asymptomatic' aortic stenosis seen at a referral center is heterogeneous. A few patients are misdiagnosed as being asymptomatic, and others have left ventricular dysfunction indicating maladaptation to the chronic pressure overload, although no symptoms are reported. Further postponement of AVR in these patients is like-

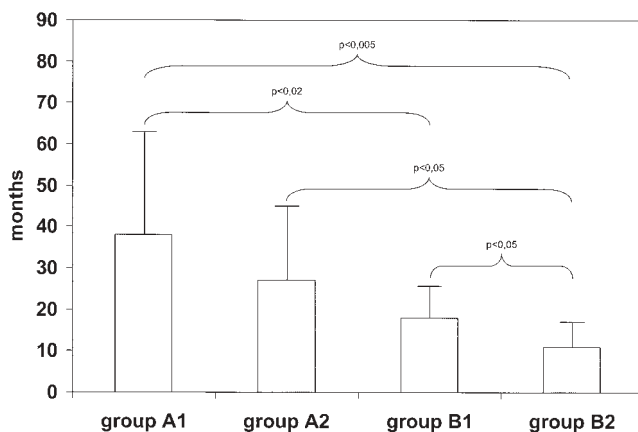


Figure 2: Time interval until manifestation of classical symptoms in the four subgroups A1, A2, B1 and B2.

ly to result in irreversible myocardial dysfunction (15-18). These findings highlight that the traditional approach, focusing on classical symptoms only for recommendation of surgical intervention, is inappropriate at least in some cases, and that additional parameters indicating myocardial adaptation and postoperative prognosis must be identified (1,2,4,15,18).

An abnormal response to exercise testing and severe calcification of the aortic valve cusps have been proven to indicate rapid progression of aortic valve obstruction with a short interval until the as-yet asymptomatic patients present with classical symptoms (4,19,20). Similar results emerged in the present study for atypical symptoms and electrocardiographic signs of left ventricular hypertrophy or ST-segment/T-wave abnormalities. The electrocardiographic abnormalities led to a statistically significant decrease in the time interval until manifestation of classical symptoms in patients who already exhibited atypical symptoms, but not in entirely asymptomatic patients.

As atypical symptoms and electrocardiographic abnormalities had no influence on the postoperative outcome in this study, the presence of these parameters alone does not allow any recommendation for surgical intervention. Further studies with greater numbers of patients and longer follow up periods may be necessary to clarify this issue. Atypical symptoms and the abnormalities in the resting electrocardiogram analyzed in the present study can be employed to estimate clinical and hemodynamic progression and to set appropriate intervals for follow up examinations. In particular, patients with both atypical symptoms and ST-segment/T-wave abnormalities or electrocardiographic signs of left ventricular hypertrophy require close clinical surveillance, as they are likely to experience classical symptoms necessitating AVR within one year.

### Study limitations

Because most study patients were either treated medically or underwent AVR before classical symptoms had developed, the subgroups of those who were followed from an asymptomatic state until manifestation of classical symptoms were small in number. The indications for earlier valve replacement surgery were based on individual decisions, which were sometimes not in accordance with current guidelines (1,2). No attempt was made to lay down precise definitions for the atypical symptoms investigated in this study, because the authors believe that these symptoms are naturally unspecific and may sometimes be indistinguishable from constitutional abnormalities. Unlike palpitations, arrhythmias are - strictly speaking - not a symptom. However, for the purpose of this pilot study,

and from a practical point of view, it appeared useful to combine palpitations with arrhythmias and to record a variety of different rhythm disturbances. Exercise stress testing is increasingly used as a diagnostic tool in asymptomatic patients (19,20), and the association between atypical symptoms, electrocardiographic signs and the results of stress testing might be of particular interest and allow more insight into the natural history of aortic valve stenosis. Exercise stress testing, however, was not performed on a regular basis in the present patient population.

Despite these limitations, it is believed that the results of this study are pertinent, and should encourage further research to define the role of atypical symptoms and electrocardiographic abnormalities in comparison with classical symptoms of hemodynamically severe aortic stenosis, which necessitate urgent valve replacement.

*In summary*, the presence of atypical symptoms such as dizziness, exertional intolerance, fatigue, palpitations or documented arrhythmias as well as electrocardiographic signs of left ventricular hypertrophy or ST-segment/T-wave deviations in otherwise asymptomatic individuals with moderate to severe aortic stenosis indicates that classical symptoms of advanced aortic stenosis (exertional dyspnea/congestive heart failure, angina pectoris, syncope) are likely to occur soon. The aortic valve area decreases more rapidly in comparison with patients who are entirely asymptomatic.

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