

## PREDICTORS OF OUTCOME IN SEVERE, ASYMPTOMATIC AORTIC STENOSIS

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**ABSTRACT**

**Background** Whether to perform valve replacement in patients with asymptomatic but severe aortic stenosis is controversial. Therefore, we studied the natural history of this condition to identify predictors of outcome.

**Methods** During 1994, we identified 128 consecutive patients with asymptomatic, severe aortic stenosis (59 women and 69 men; mean [ $\pm$ SD] age,  $60\pm 18$  years; aortic-jet velocity,  $5.0\pm 0.6$  m per second). The patients were prospectively followed until 1998.

**Results** Follow-up information was available for 126 patients (98 percent) for a mean of  $22\pm 18$  months. Event-free survival, with the end point defined as death (8 patients) or valve replacement necessitated by the development of symptoms (59 patients), was  $67\pm 5$  percent at one year,  $56\pm 5$  percent at two years, and  $33\pm 5$  percent at four years. Five of the six deaths from cardiac disease were preceded by symptoms. According to multivariate analysis, only the extent of aortic-valve calcification was an independent predictor of outcome, whereas age, sex, and the presence or absence of coronary artery disease, hypertension, diabetes, and hypercholesterolemia were not. Event-free survival for patients with no or mild valvular calcification was  $92\pm 5$  percent at one year,  $84\pm 8$  percent at two years, and  $75\pm 9$  percent at four years, as compared with  $60\pm 6$  percent,  $47\pm 6$  percent, and  $20\pm 5$  percent, respectively, for those with moderate or severe calcification. The rate of progression of stenosis, as reflected by the aortic-jet velocity, was significantly higher in patients who had cardiac events ( $0.45\pm 0.38$  m per second per year) than those who did not have cardiac events ( $0.14\pm 0.18$  m per second per year,  $P<0.001$ ), and the rate of progression of stenosis provided useful prognostic information. Of the patients with moderately or severely calcified aortic valves whose aortic-jet velocity increased by 0.3 m per second or more within one year, 79 percent underwent surgery or died within two years of the observed increase.

**Conclusions** In asymptomatic patients with aortic stenosis, it appears to be relatively safe to delay surgery until symptoms develop. However, outcomes vary widely. The presence of moderate or severe valvular calcification, together with a rapid increase in aortic-jet velocity, identifies patients with a very poor prognosis. These patients should be considered for early valve replacement rather than have surgery delayed until symptoms develop. (N Engl J Med 2000; 343:611-7.)

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**T**HE poor outcome of patients with symptomatic aortic stenosis has been well documented.<sup>1-10</sup> In view of the excellent results of aortic-valve replacement,<sup>2,11-16</sup> surgery is strongly recommended for these patients.<sup>17</sup> In contrast, the management of asymptomatic aortic stenosis remains controversial.<sup>17</sup> The occurrence of sudden death without preceding symptoms<sup>14,18</sup> and the potential risk of irreversible myocardial damage<sup>14,19</sup> argue for early elective surgery. However, prospective studies suggest that, in the absence of preceding symptoms, sudden death may be uncommon.<sup>20,21</sup> Nevertheless, in 1997, Otto et al. reported rapid progression and poor outcomes among patients with asymptomatic aortic stenosis,<sup>22</sup> again raising the question of early elective surgery.<sup>23</sup> Considering the wide variation in individual outcomes, the potential risk of complications related to the prosthetic valve,<sup>17,24-30</sup> and the risk of valve surgery itself, the decision whether to operate on an asymptomatic patient remains difficult. The identification of predictors of outcome that could help in the selection of patients who are likely to benefit from early surgery would be highly desirable. We therefore prospectively studied a large cohort of patients with asymptomatic, severe aortic stenosis to identify clinical or echocardiographic predictors of outcome.

**METHODS****Patients**

All patients who were studied in our echocardiography laboratory between January 1 and December 31, 1994, and who were found to have a stenotic native aortic valve with a peak aortic-jet velocity of at least 4 m per second were included in the study if they had no additional hemodynamically significant valvular lesions and if they presented without symptoms. As in previous studies,<sup>20</sup> patients who had mild fatigue or mild dyspnea during maximal exercise were not excluded, because of the lack of specificity of these symptoms. Written informed consent was obtained from the patients for all procedures that were performed.

One hundred twenty-eight patients (mean [ $\pm$ SD] age,  $60\pm 18$  years; 59 women and 69 men; mean aortic-jet velocity,  $5.0\pm 0.6$  m per second) were identified by these criteria. All patients had normal left ventricular function, except for two with coronary artery disease. In these two patients, wall-motion abnormalities were regional rather than global and apparently were related to coronary artery disease, as demonstrated by coronary angiography. According

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to color Doppler ultrasonography, additional mild aortic regurgitation was present in 70 patients and mild-to-moderate or moderate aortic regurgitation in 33. The valve area of these 33 patients was 0.8 cm<sup>2</sup> or less, and none had signs of left ventricular volume overload or clinical signs of hemodynamically relevant aortic regurgitation. Eighty-four patients had mild mitral regurgitation, and 61 had mild tricuspid regurgitation; 8 patients also had mild mitral stenosis.

### Echocardiography

Echocardiographic data were obtained with the use of commercially available ultrasound systems. All patients underwent a comprehensive examination, including M-mode echocardiography, two-dimensional echocardiography, and conventional and color Doppler ultrasonography, conducted by an experienced echocardiographer. Valve stenosis was defined as congenital if there was clear identification of two cusps in systole and systolic cusp doming or highly asymmetric thickening or both; it was defined as rheumatic if there was commissural fusion and mitral-valve involvement; and it was defined as degenerative if there was thickening and increased echogenicity of the cusps (excluding the free edges), with reduced systolic opening. The degree of calcification of the aortic valve was scored as follows: 1, no calcification; 2, mildly calcified (small isolated spots); 3, moderately calcified (multiple larger spots); and 4, heavily calcified (extensive thickening and calcification of all cusps). Mitral annular calcification was defined as a dense, highly reflective area at the base of the mitral-valve leaflets. For all patients for whom at least two echocardiographic studies, separated by at least six months, were available, the mean increase in aortic-jet velocity (in meters per second per year) was calculated by dividing the difference between the velocities measured at the first and last examinations by the time between examinations.

### Follow-up

The patients were followed prospectively, beginning with the visit in 1994. Follow-up information was obtained from interviews with the patients, their relatives, and their physicians. We collected information regarding the development of cardiac symptoms, eventual aortic-valve replacement, and mortality.

For the assessment of outcome, the end point was death or aortic-valve replacement necessitated by the development of symptoms. Deaths were classified as due or not due to cardiac causes on the basis of discussion with the primary care physician (two deaths), review of medical records (two deaths), or review of medical records including autopsy records (four deaths). Deaths due to cardiac causes were further classified as directly related to aortic stenosis (sudden death or death from congestive heart failure) or as related to other cardiac conditions. To evaluate the overall outcome of patients treated according to a "wait for symptoms" strategy, we also followed patients who underwent surgery because of the development of symptoms until 1998 and obtained information regarding perioperative and late mortality.

### Statistical Analysis

The results are given as means  $\pm$ SD, except for Kaplan–Meier estimates, for which the standard error is given. Base-line differences between the groups undergoing and not undergoing surgery were analyzed by a two-sample t-test or a chi-square test for equality of proportions, when appropriate. Data on event-free survival were analyzed by the Kaplan–Meier method.

Data on overall survival, as determined at the last follow-up in 1998 (taking into account perioperative deaths and postoperative follow-up for patients who required surgery because of the development of symptoms), were also analyzed and compared with control data on survival among persons of the same age and sex. The control data were obtained from Austrian life tables for 1992, which were provided by the Austrian Statistical Institute and represent the survival of the general Austrian population.

The effects of clinical variables (age, sex, and presence or absence of coronary artery disease, hypertension, diabetes, and hypercholesterolemia) and echocardiographic variables (degree of aortic-

valve calcification, cause of stenosis, and aortic-jet velocity) were analyzed by the Kaplan–Meier method. Statistical significance was determined by the log-rank test. For multivariate analysis, a Cox proportional-hazards model was used. A P value of less than 0.05 was considered to indicate statistical significance.

## RESULTS

Of the total study group, 22 patients, although remaining asymptomatic, underwent aortic-valve replacement within three months after examination at the discretion of their referring cardiologist (the surgical group). The remaining 106 patients (the nonsurgical group) were followed for  $27 \pm 17$  months. In this group, surgery was delayed until symptoms developed. The characteristics of the patients in the surgical and nonsurgical groups are shown in Table 1. On average, the patients in the nonsurgical group were younger and had a lower aortic-jet velocity. However, the ages and velocities in the surgical group were well represented in the nonsurgical group.

### Outcome for the Total Study Group

Follow-up information was available for 126 patients (98 percent). Data on the 22 patients in the surgical group were censored at the time of valve replacement.

### Event-free Survival

During a mean follow-up period of  $22 \pm 18$  months (range, 0 to 54), 67 end points were observed, including 8 deaths and 59 valve replacements performed because of the development of symptoms. Event-free survival was  $67 \pm 5$  percent at one year,  $56 \pm 5$  percent at two years, and  $33 \pm 5$  percent at four years.

### Deaths

Six of the eight deaths were due to cardiac causes (four to congestive heart failure, one to endocarditis, and one sudden death). All deaths from cardiac causes were presumed to be related to aortic stenosis. Except for the one sudden death, they were all preceded by the development of symptoms. Aortic-valve replacement was not performed in these patients for the following reasons: three patients refused to have surgery, one had advanced prostatic cancer, and one died awaiting surgery. Of the two deaths from other causes, one was due to pulmonary embolism and the other to acute myeloid leukemia.

### Surgery

Fifty-nine patients underwent aortic-valve replacement because symptoms developed. These patients were followed postoperatively for  $28 \pm 15$  months. Of the five deaths among these patients, four occurred perioperatively and one was not due to cardiac causes. The remaining 54 patients were alive at the end of the study in 1998.

### Overall Survival

The overall actuarial probability of survival ( $\pm$ SE) at the end of the study in 1998 was  $93 \pm 2$  percent

**TABLE 1.** CHARACTERISTICS OF 128 PATIENTS WITH ASYMPTOMATIC AORTIC STENOSIS ACCORDING TO WHETHER THEY UNDERWENT AORTIC-VALVE REPLACEMENT WITHIN THREE MONTHS AFTER EXAMINATION.\*

CHARACTERISTIC	SURGICAL GROUP (N=22)	NONSURGICAL GROUP (N=106)	P VALUE
Female sex — no. (%)	11 (50)	48 (45)	NS
Age — yr			
Mean	71±12	57±19	<0.001
Range	37–88	15–87	
Aortic-jet velocity — m/sec			
Mean	5.0±0.7	4.5±0.5	<0.005
Range	4.0–6.1	4.0–6.5	
Aortic-valve area — cm <sup>2</sup>			
Mean	0.61±0.13	0.69±0.10	<0.01
Range	0.4–0.8	0.4–0.8	
Coronary artery disease — no. (%)	5 (23)	28 (26)	NS
Hypertension — no. (%)	7 (32)	37 (35)	NS
Diabetes mellitus — no. (%)	4 (18)	19 (18)	NS
Hypercholesterolemia — no. (%)	17 (77)	52 (49)	<0.05
Mitral annular calcification — no. (%)	10 (45)	37 (35)	NS

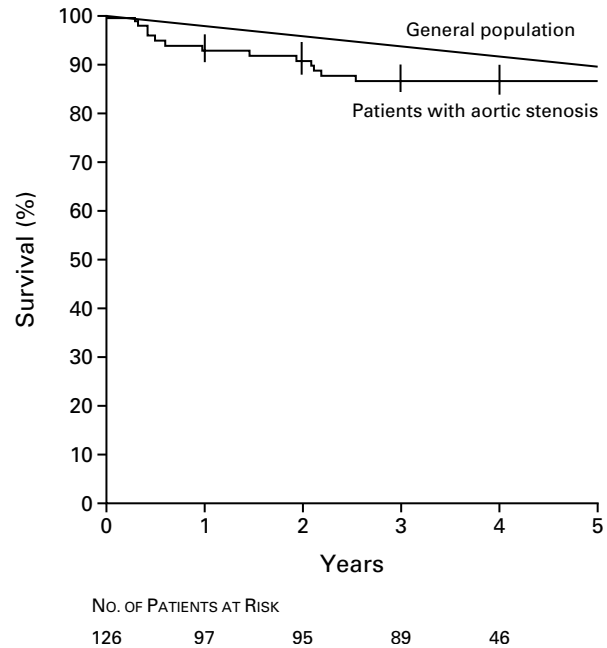
\*Plus-minus values are means ±SD. NS denotes not significant.

at one year, 91±3 percent at two years, and 87±3 percent at four years (Fig. 1). Survival was slightly worse than that of an age- and sex-matched population, but the difference was not significant.

**Predictors of Outcome**

According to univariate analysis, an age of more than 50 years, diabetes mellitus, and coronary artery disease were predictors of subsequent cardiac events, whereas the effects of female sex, hypertension, and hypercholesterolemia did not reach statistical significance (Table 2). When only clinical data were considered, an older age remained the only significant predictor of outcome according to the multivariate analysis. Event-free survival for patients 50 years of age or younger was 85±6 percent at one year, 69±8 percent at two years, and 59±9 percent at four years. In comparison, the event-free survival rates for patients older than 50 years were 59±6 percent, 49±6 percent, and 21±5 percent at one, two, and four years, respectively (Fig. 2).

The extent of aortic-valve calcification was a strong predictor of subsequent events (P<0.001). Event-free survival for patients with no or mild calcification was 92±5 percent at one year, 84±8 percent at two years, and 75±9 percent at four years, as compared with 60±6 percent, 47±6 percent, and 20±5 percent, respectively, for those with moderate or severe calcification (Fig. 3). The outcome was almost identical for patients with moderate calcification and for those with severe calcification. All deaths occurred among these patients. The best outcome was found



**Figure 1.** Kaplan–Meier Analysis of Overall Survival among 126 Patients with Asymptomatic but Severe Aortic Stenosis, as Compared with Age- and Sex-Matched Persons in the General Population.

This analysis included perioperative and postoperative deaths among patients who required valve replacement during follow-up. The vertical bars indicate standard errors.

for patients without calcification; among 11 such patients, no event occurred during a mean follow-up of 38±16 months. Of the 25 patients with no or only mild calcification, 21 had congenital disease and 4 had rheumatic disease. However, the cause of stenosis was difficult to assess in the presence of moderate or severe calcification and therefore frequently remained uncertain. Thus, the assessment of the cause of stenosis did not provide useful prognostic information.

On average, the aortic-jet velocity was only slightly higher in patients who had cardiac events during follow-up than in those who did not (4.66±0.62 vs. 4.41±0.38 m per second). This difference was statistically significant (P=0.03). Nevertheless, the aortic-jet velocity was not a significant predictor of subsequent cardiac events. However, the rate of progression of aortic-jet velocity was significantly higher in patients who had cardiac events than in those who did not have such events (0.45±0.38 vs. 0.14±0.18 m per second per year, P<0.001) (Fig. 4).

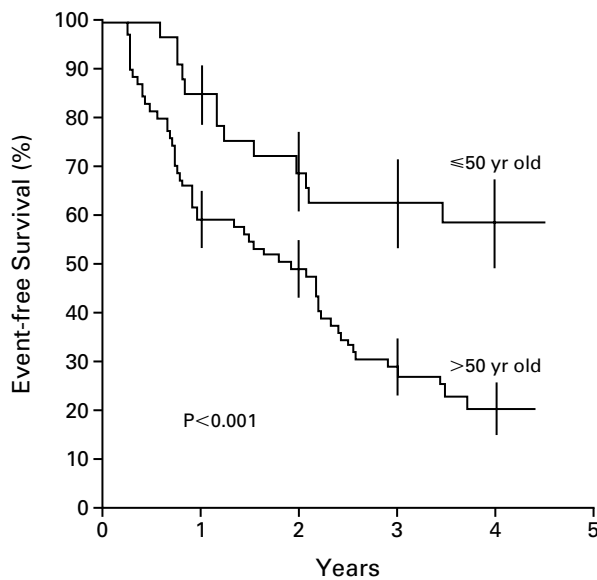
When clinical and echocardiographic data were considered together in a multivariate analysis, the extent of valvular calcification was the only independent predictor of outcome. Ninety of the 93 patients over 50 years of age (97 percent) presented with moder-

**TABLE 2. RESULTS OF UNIVARIATE AND MULTIVARIATE ANALYSIS OF CLINICAL AND ECHOCARDIOGRAPHIC PREDICTORS OF OUTCOME.\***

VARIABLE	No. OF PATIENTS WITH VARIABLE (%)	UNIVARIATE ANALYSIS		MULTIVARIATE ANALYSIS	
		P VALUE	RISK RATIO (95% CI)	P VALUE	RISK RATIO (95% CI)
Age >50 yr	93 (74)	<0.001	2.7 (1.5–5.2)	NS	1.1 (0.5–2.6)
Female sex	59 (47)	NS	0.9 (0.7–1.2)	NS	0.9 (0.7–1.2)
Coronary artery disease	33 (26)	<0.05	1.7 (1.0–2.9)	NS	1.1 (0.6–1.9)
Hypertension	44 (35)	NS	0.9 (0.5–1.5)	NS	0.6 (0.4–1.1)
Diabetes	23 (18)	<0.05	1.9 (1.0–3.3)	NS	1.3 (0.7–2.5)
Hypercholesterolemia	69 (55)	NS	1.2 (0.7–2.0)	NS	1.0 (0.6–1.7)
Aortic-jet velocity $\geq 4.5$ m/sec	64 (51)	NS	1.3 (0.8–2.1)	NS	1.1 (0.7–1.9)
Aortic-valve calcification score 3 or 4†	101 (80)	<0.001	5.2 (2.4–13.5)	<0.01	4.6 (1.6–14.0)

\*Data are for 126 of the 128 patients; the remaining 2 patients were lost to follow-up. CI denotes confidence interval, and NS denotes not significant. Risk ratios are for the occurrence of an event (death or valve replacement).

†A score of 3 indicated moderate calcification, and a score of 4 heavy calcification.



NO. OF PATIENTS AT RISK		0	1	2	3	4	5
≤50 yr	33	29	23	20	9		
>50 yr	93	43	36	19	7		

**Figure 2.** Kaplan–Meier Analysis of Event-free Survival among 33 Patients 50 Years of Age or Younger, as Compared with 93 Patients over 50 Years of Age.

The vertical bars indicate standard errors.

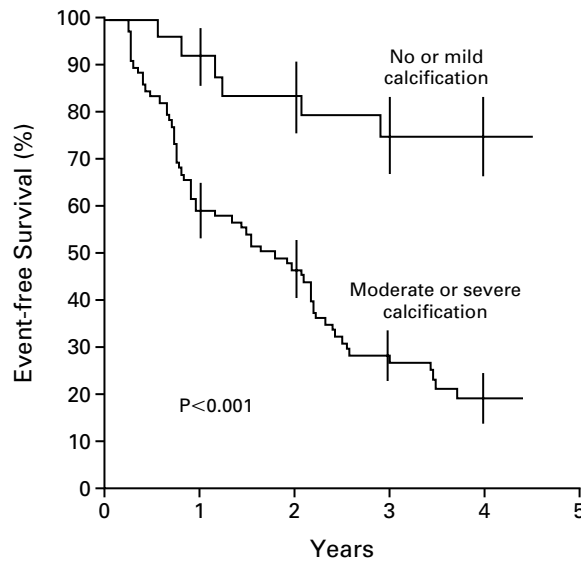
ate or severe aortic-valve calcification. Although the majority of patients 50 years of age or younger had less calcified valves, 33 percent of them presented with moderate or severe calcification. These patients had event-free survival very similar to that among patients over 50 years of age who had moderately or

severely calcified valves. The rate of progression of aortic-jet velocity added useful prognostic information to the classification based on the degree of calcification. The combination of calcification and a rapid increase in aortic-jet velocity identified a high-risk group. Of the patients with moderately or severely calcified valves who had an increase of 0.3 m per second or more within one year, 79 percent underwent surgery because of new symptoms or died within two years (Fig. 5). In this analysis, follow-up started at the time of the visit at which this rapid increase in velocity was recognized in an otherwise asymptomatic patient.

### DISCUSSION

Many physicians are reluctant to refer patients with severe aortic stenosis for valve replacement as long as they remain asymptomatic.<sup>23</sup> However, there remains concern about the risk of irreversible myocardial damage<sup>14,19</sup> or sudden death among such patients who do not undergo surgery. In contrast to patients with valvular regurgitation, patients with severe aortic stenosis who are still asymptomatic but already have impaired left ventricular function are very rare. Nevertheless, myocardial fibrosis or severe hypertrophy may not be reversible after delayed surgery and may preclude an optimal postoperative outcome. However, the outcome after valve replacement is excellent in patients with normal preoperative left ventricular function.<sup>2,11-16</sup> Therefore, the potential benefit of preventing myocardial fibrosis and severe hypertrophy by early intervention is unlikely to outweigh the risk of perioperative and late complications of valve replacement in asymptomatic patients.

Sudden death in patients with aortic stenosis is an issue of concern. Prospective data on sudden death



NO. OF PATIENTS AT RISK					
No or mild calcification	25	23	20	17	9
Moderate or severe calcification	101	48	38	21	7

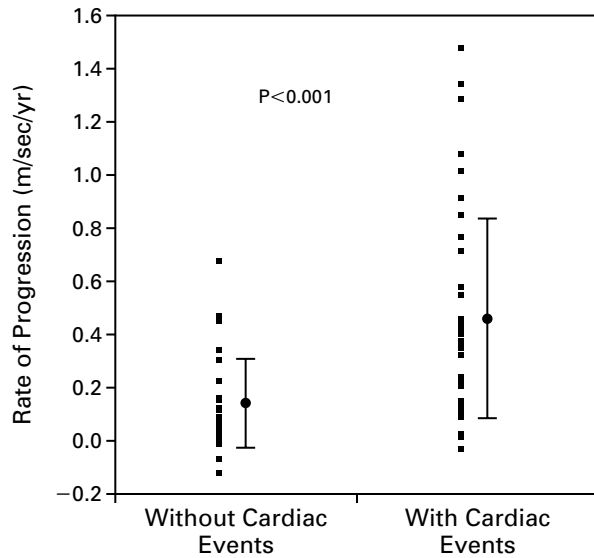
**Figure 3.** Kaplan–Meier Analysis of Event-free Survival among 25 Patients with No or Mild Aortic-Valve Calcification, as Compared with 101 Patients with Moderate or Severe Calcification. The vertical bars indicate standard errors.

are limited. Otto et al.<sup>22</sup> followed 123 patients for an average of 30 months and reported no sudden deaths, but the majority of these patients did not have severe aortic stenosis. In two small series<sup>6,21</sup> with follow-up periods of 1.5 and 2.0 years, there were also no sudden deaths without preceding symptoms, but again, a considerable percentage of patients did not have severe stenosis. The only study that followed a larger cohort of patients with severe stenosis was conducted by Pellikka et al.<sup>20</sup> During a mean follow-up of 20 months, there were two sudden deaths, but symptoms had developed in both patients at least 3 months before death. In our series of 126 patients with slightly higher aortic-jet velocities and a longer follow-up (27 months), one sudden death occurred, which was not preceded by any symptoms. Thus, our study supports the idea that sudden death may occur even in the absence of preceding symptoms in patients with aortic stenosis, but that it appears to be uncommon, with an incidence of probably less than 1 percent per year.<sup>17</sup>

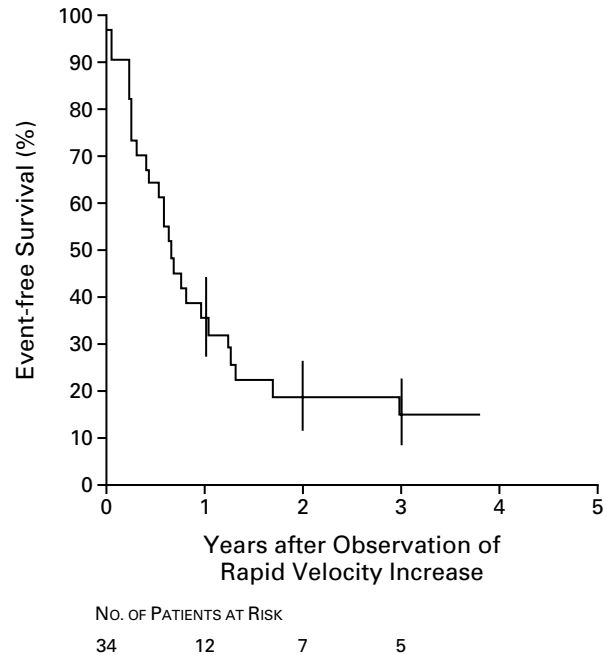
Although Pellikka et al.<sup>20</sup> reported no deaths related to aortic stenosis without preceding symptoms, 3 of 113 patients eventually died of aortic stenosis during a mean follow-up of 20 months. It is possible that these patients did not promptly report the development of symptoms or that they died while waiting for surgery, as was the case in one patient in the

present study. According to another report,<sup>31</sup> 7 of 99 patients with severe aortic stenosis who were scheduled for surgery died during an average waiting period of six months. In addition, patients with severe symptoms have been found to have significantly higher operative mortality than those with no symptoms or only mild ones, and surgery performed as an urgent procedure carries a higher risk than elective surgery.<sup>32</sup>

Thus, the possibility that patients may not report symptoms promptly and that logistic problems may delay surgery, as well as the higher operative mortality for patients with symptoms and those undergoing urgent surgery, makes it highly desirable to identify patients in whom symptoms are likely to develop and who require surgery within a very short period, since such patients would benefit from early elective aortic-valve replacement. In the study by Pellikka et al.,<sup>20</sup> only aortic-jet velocity and ejection fraction were independent predictors of the risk of subsequent cardiac events, whereas age, sex, and the presence or absence of hypertension, diabetes mellitus, left ventricular hypertrophy, electrocardiographic strain pattern, ventricular ectopic activity, and coronary artery disease, smoking status, and the use or nonuse of digoxin or diuretic drugs were not. In the study by Otto et al.,<sup>22</sup> the only predictors of outcome were aortic-jet velocity, the rate of change in this velocity, and functional status, but not age, sex, cause of aortic steno-



**Figure 4.** Mean Rate of Progression of Aortic-Jet Velocity among 41 Patients Who Had Cardiac Events and 29 Who Did Not. The bars represent means  $\pm$ SD.



**Figure 5.** Kaplan–Meier Analysis of Event-free Survival among 34 Patients with Moderate or Severe Calcification of the Aortic Valve and a Rapid Increase in Aortic-Jet Velocity (at Least 0.3 m per Second within One Year).

In this analysis, follow-up started with the visit at which the rapid increase was identified. The vertical bars indicate standard errors.

sis, left ventricular mass, or ejection fraction. Neither of these studies allowed any conclusions to be drawn about how to select high-risk patients who might benefit from early elective surgery.

In the present study, in agreement with previous reports,<sup>20,22</sup> we did not identify any clinical variable as an independent predictor of subsequent cardiac events. However, the extent of valvular calcification was found to be a strong independent predictor of outcome. As in previous reports, aortic-jet velocity was significantly higher in patients who had cardiac events, but the difference was small, and the marked overlap precludes drawing any conclusions about outcome for an individual patient. However, our results suggest that assessment of the rate of progression of aortic-jet velocity by serial echocardiographic examination may yield important prognostic information in addition to the degree of calcification. Thus, although not generally recommended in the recently published practice guidelines,<sup>17</sup> annual echocardiographic studies may play an important part in the management of asymptomatic aortic stenosis.

A limitation of our study is that 22 patients underwent surgery within three months after examination, although they were still asymptomatic. It may be almost impossible, however, to study the outcome of a large cohort of patients with severe but asymptomatic aortic stenosis without encountering this problem.<sup>20,22</sup> Although current practice guidelines<sup>17</sup> do not recommend surgery for asymptomatic patients with severe aortic stenosis, their optimal treatment re-

mains controversial, and some physicians decide to refer their patients for valve replacement despite the lack of data to support this strategy. Although the patients in the nonsurgical group were, on average, younger and had, on average, lower aortic-jet velocities, the ages and velocities in the surgical group were well represented in the nonsurgical group. The groups did not differ in any other respect.

In conclusion, our study confirms that in patients with hemodynamically significant aortic stenosis, it is relatively safe to delay surgery until symptoms develop. However, sudden death can occur even without preceding symptoms, although this is rare. Death may also occur in newly symptomatic patients who do not promptly report symptoms or who are awaiting surgery. In addition, the risk entailed by surgery is higher in symptomatic than in asymptomatic patients. Echocardiography appears helpful in the management of asymptomatic aortic stenosis, since it permits the early identification of patients at risk.

Patients with no or only mild calcification of their stenotic aortic valves represent a low-risk subgroup. They may remain asymptomatic for many years, and early elective surgery is definitely not justified. Fol-

low-up visits at annual intervals and instruction to report the development of symptoms promptly appear to be appropriate for these patients. In contrast, patients with severe, asymptomatic aortic stenosis and moderately or severely calcified valves represent a subgroup of patients with a poorer prognosis. Rapid progression of the disease can be expected, and approximately 80 percent of these patients will require valve replacement or die within four years. Thus, such patients must be followed with special care. Even in this group, however, individual outcomes vary widely, and elective surgery cannot be generally recommended.

In patients with moderately or severely calcified valves in whom serial echocardiographic testing reveals a marked increase in aortic-jet velocity, the outcome is significantly worse, and an 80 percent event rate at two years can be expected. Because patients do not always report symptoms promptly, and in consideration of the elevated risk of death while patients await surgery, as well as the higher operative risk in symptomatic patients and those undergoing urgent surgery, it may be worthwhile to consider early elective valve replacement instead of waiting for symptoms to develop in this high-risk group.

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