Outcome of 622 Adults With Asymptomatic, Hemodynamically Significant Aortic Stenosis During Prolonged Follow-Up

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Background—This study assessed the long-term outcome of a large, asymptomatic population with hemodynamically significant aortic stenosis (AS).

Methods and Results—We identified 622 patients with isolated, asymptomatic AS and peak systolic velocity ≥4 m/s by Doppler echocardiography who did not undergo surgery at the initial evaluation and obtained follow-up (5.4±4.0 years) in all. Mean age (±SD) was 72±11 years; there were 384 (62%) men. The probability of remaining free of cardiac symptoms while unoperated was 82%, 67%, and 33% at 1, 2, and 5 years, respectively. Aortic valve area and left ventricular hypertrophy predicted symptom development. During follow-up, 352 (57%) patients were referred for aortic valve surgery and 265 (43%) patients died, including cardiac death in 117 (19%). The 1-, 2-, and 5-year probabilities of remaining free of surgery or cardiac death were 80%, 63%, and 25%, respectively. Multivariate predictors of all-cause mortality were age (hazard ratio [HR], 1.05; P<0.0001), chronic renal failure (HR, 2.41; P=0.004), inactivity (HR, 2.00; P=0.001), and aortic valve velocity (HR, 1.46; P=0.03). Sudden death without preceding symptoms occurred in 11 (4.1%) of 270 unoperated patients. Patients with peak velocity ≥4.5 m/s had a higher likelihood of developing symptoms (relative risk, 1.34) or having surgery or cardiac death (relative risk, 1.48).

Conclusions—Most patients with asymptomatic, hemodynamically significant AS will develop symptoms within 5 years. Sudden death occurs in ~1%/y. Age, chronic renal failure, inactivity, and aortic valve velocity are independently predictive of all-cause mortality. (Circulation. 2005;111:3290-3295.)

Key Words: echocardiography • surgery • survival • valves • aortic stenosis

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In a previous study of 113 patients with asymptomatic aortic stenosis (AS) and peak systolic flow velocity ≥4 m/s who were followed up for a mean of 20 months, we noted that no patients had sudden death or cardiac death without preceding symptoms. In addition, the survival of this group was comparable to that of age- and sex-matched controls. Other studies involving smaller numbers of asymptomatic patients have also suggested that these patients are at low risk and that surgical treatment can be postponed until symptoms appear, without a significant risk of sudden death.

AS is a chronic and progressive disease. Long-term follow-up in a large population is necessary to characterize the natural history of this disorder. Moreover, it is recognized that infrequently occurring events may not occur in a small population. In the previous studies, the numbers of patients with severe AS were small. In those patients, the risk of sudden death was presumably >0 but might have been difficult to assess in a small sample. Furthermore, the duration of follow-up was <2 years in most studies. Therefore, management of the patient with asymptomatic, hemodynamically significant AS remains uncertain.

The purpose of the present study was to evaluate the natural history of asymptomatic, hemodynamically significant valvular AS in adults in a large population with extended follow-up. Specifically, we sought to determine the following: (1) the rate of development of symptoms and the characteristics predicting the development of symptoms in the unoperated patient; (2) the risk and predictors of all-cause mortality in patients who present with asymptomatic AS; and (3) the risk of sudden death, preceded by symptoms, in the unoperated patient.

Methods

Study Patients
From 1984 to 1995, 2853 patients ≥40 years of age with valvular AS and a peak systolic velocity ≥4 m/s by Doppler echocardiography were identified by retrospective review of our database. All patients were evaluated by a cardiologist, or an internist in consultation with...
a cardiologist. One thousand one hundred eighty-one patients were excluded from this study for the following reasons: (1) multivalvular involvement, (2) moderate to severe aortic regurgitation, (3) documented myocardial infarction, (4) prior coronary artery bypass grafting or percutaneous transluminal coronary angioplasty, (5) prior percutaneous aortic balloon valvuloplasty, or (6) prior valve replacement or cardiac surgery. Among the remaining 1672 patients, 968 were excluded from further study because of a history of cardiac symptoms, including angina, dyspnea, syncope, presyncope, or congestive heart failure reported at the time of the initial clinical and echocardiographic evaluations. Patients with fatigue or mild dyspnea occurring with maximal exertion were not excluded because of the nonspecificity of the symptoms. Ten additional patients were excluded because they denied access to medical records. Seventy-two patients (mean±SD age, 70±11 years; peak aortic valve systolic velocity, 4.8±0.6 m/s; mean gradient, 54±12 mm Hg; Doppler-derived aortic valve area, 0.69±0.17 cm²) were excluded because they were referred to surgery on the basis of the initial evaluation. The remaining 622 patients formed the study group. The present study includes the 113 patients in whom intermediate follow-up data were previously reported.1 These patients were advised to return for reevaluation at 6 months or 1 year and to return promptly at the onset of symptoms.

Activity level was classified as inactive (assisted care) or active (living independently). Other clinical factors recorded included hypertension, diabetes mellitus, cigarette smoking, renal failure (defined as creatinine >2 mg/dL), digoxin therapy, β-adrenergic blocker therapy, calcium antagonist therapy, and diuretic drug use. The ECG was analyzed for left ventricular hypertrophy according to the criteria of Romhilt and Estes.6

### Echocardiographic and Doppler Measurements

All patients underwent a comprehensive 2-dimensional and Doppler echocardiographic evaluation between 1984 and 1995. Left ventricular ejection fraction was calculated by measuring the left ventricular short axis with a modification of the method of Quinones et al.7 Continuous-wave Doppler examinations were performed with a nonimaging transducer and multiple windows to obtain the maximal jet velocity. The maximal instantaneous and mean pressure gradients across the aortic valve were calculated with a modified Bernoulli equation. In patients with atrial fibrillation, velocities from 10 consecutive beats were averaged. The aortic valve area was calculated from the continuity equation.8,9 In patients with atrial fibrillation, velocities from 10 consecutive beats were averaged. The aortic valve area was calculated from the continuity equation by using the left ventricular outflow diameter and velocity. The valve area was determined in 293 (47%) patients; during the earlier period of the study, it was not routine practice to determine a Doppler-derived aortic valve area.

### Follow-Up

Clinical information was obtained by mailed questionnaires, review of medical records, and scripted telephone interviews. Information about the development of cardiac symptoms, including angina, dyspnea or syncope, subsequent aortic valve surgery, and mortality, was obtained. Events were verified by review of medical records and death certificates. Deaths were classified as either cardiac or noncardiac. Death occurring without explanation was considered cardiac death. We also recorded the occurrence of sudden death, unprecedented by symptoms at any time.

### Statistical Analysis

The probability of developing cardiac symptoms in the patient untreated with surgery, the probability of death in the unoperated patient, and the probability of remaining free of cardiac death or aortic valve surgery were analyzed with the Kaplan-Meier method. The effect of the clinical, electrocardiographic, and echocardiographic variables on the development of symptoms, censored (follow-up included until this event) at aortic valve surgery, and on all-cause mortality, also censored at surgery, were studied with Cox proportional-hazards regression analysis. Survival of patients with AS, censoring at symptom onset and at aortic valve surgery, was compared with that of the Minnesota white population matched for age and sex (referent group) and tested with the 1-sample log-rank test. This comparison was repeated, this time censoring only for aortic valve surgery but not for symptoms.

### Results

#### Population and Follow-Up

There were 384 (62%) men and 238 (38%) women; the mean±SD age was 72±11 years. Clinical and echocardiographic characteristics of the population are shown in Table 1. The peak velocity averaged 4.4±0.4 m/s (range, 4.0 to 6.6), and the mean gradient was 46±11 mm Hg (range, 21 to 107). Mean aortic valve area was 0.9±0.2 cm² (range, 0.38 to 1.80). Follow-up was obtained for all patients. The mean duration of follow-up was 5.4±4.0 years (maximum, 15).

#### Development of Symptoms

During follow-up, 297 (50%) patients developed symptoms of angina, dyspnea, or syncope before any aortic valve surgery. The Kaplan-Meier probability of remaining free of cardiac symptoms while unoperated was 82% at 1 year, 67% at 2 years, and 33% at 5 years (Figure 1).

The univariate models for development of symptoms are shown in Table 2. Aortic valve area (hazard ratio [HR], 0.33 for a 1-cm² increase; 95% confidence interval [CI], 0.15 to 0.71; \( P = 0.005 \)) and left ventricular hypertrophy (HR, 1.39; 95% CI, 1.02 to 1.89; \( P = 0.04 \)) were the only independent predictors of the development of symptoms in multivariate analysis.
Aortic Valve Replacement, All-Cause Mortality, and Cardiac Death

Three hundred fifty-two (57%) patients underwent aortic valve surgery; this included 221 who had developed symptoms and 131 who remained asymptomatic but were referred for surgery because of the recommendation of their physician (Figure 2). During follow-up, 265 (43%) patients died. Causes of death are shown in Table 3. There were 117 (19%) cardiac deaths in the 622 patients. The Kaplan-Meier probability of remaining free of cardiac events, including cardiac death or aortic valve surgery, was 80% at 1 year, 63% at 2 years, and 25% at 5 years. Univariate and multivariate models for prediction of all-cause mortality before any cardiac surgery are shown in Table 4. Age, chronic renal failure, inactivity, and aortic valve velocity predicted mortality.

Relation of Echocardiographic Parameters With Outcome

Among the 622 patients, 191 (31%) had a peak velocity ≥4.5 m/s. When these were compared with those with a peak velocity of <4.5 m/s, the relative risk (RR) of developing symptoms was 1.34 (95% CI, 1.04 to 1.72; P=0.03), and the RR of sustaining a cardiac event, including aortic valve surgery or cardiac death, was 1.48 (95% CI, 1.20 to 1.81; P=0.0002). The RR of developing symptoms per 0.2-cm² decrease in aortic valve area was 1.26 (95% CI, 1.08 to 1.47; P=0.004), and the RR of sustaining a cardiac event was 1.20 (95% CI, 1.06 to 1.36; P=0.006).

TABLE 3. Causes of Death

<table>
<thead>
<tr>
<th></th>
<th>Surgery (n=352)</th>
<th>No Surgery (n=270)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac deaths, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>12 (3.4)</td>
<td>35 (13.0)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>10 (2.8)</td>
<td>13 (4.8)</td>
</tr>
<tr>
<td>Aortic stenosis</td>
<td>...</td>
<td>18 (6.7)</td>
</tr>
<tr>
<td>Sudden death</td>
<td>6 (1.7)</td>
<td>11 (4.1)</td>
</tr>
<tr>
<td>Perioperative</td>
<td>5 (1.4)</td>
<td>...</td>
</tr>
<tr>
<td>Cardiac catheterization</td>
<td>...</td>
<td>4 (1.5)</td>
</tr>
<tr>
<td>Prosthetic valve failure</td>
<td>2 (0.5)</td>
<td>...</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>0 (0)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Noncardiac deaths</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>14 (4.0)</td>
<td>27 (10.0)</td>
</tr>
<tr>
<td>Stroke</td>
<td>9 (2.6)</td>
<td>14 (5.2)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>6 (1.7)</td>
<td>7 (2.6)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>3 (0.9)</td>
<td>9 (3.3)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>4 (1.1)</td>
<td>7 (2.6)</td>
</tr>
<tr>
<td>Malnutrition/dementia</td>
<td>2 (0.6)</td>
<td>6 (2.2)</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>2 (0.6)</td>
<td>5 (1.9)</td>
</tr>
<tr>
<td>Trauma</td>
<td>5 (1.4)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Other*</td>
<td>7 (2.0)</td>
<td>21 (7.8)</td>
</tr>
<tr>
<td>Total deaths</td>
<td>86 (24.4)</td>
<td>179 (66.3)</td>
</tr>
</tbody>
</table>

*Includes gastrointestinal bleeding, pulmonary embolism, ischemic bowel, peripheral vascular disease, diabetes mellitus, liver failure, scleroderma, and Parkinson’s disease in 5 or fewer patients each.
Cardiac Death in Asymptomatic Patients and Survival Compared With Controls

There were 11 patients with sudden death not preceded by aortic valve surgery or known symptoms. Medical follow-up was not available for 1 year or more before death in 5 of them. All other deaths attributed to AS occurred in patients with cardiac symptoms. These 11 patients included 6 men and 5 women, ranging in age from 55 to 92 years, with aortic valve velocities ranging from 4.0 to 5.8 m/s and aortic valve areas ranging from 0.53 to 1.28 cm². Four had left ventricular hypertrophy.

For patients continuing to be asymptomatic and untreated with surgery, Kaplan-Meier survival free of cardiac death was 99%, 98%, and 93% at 1, 2, and 5 years, respectively. Survival of this group, free of death from any cause, compared with that of the referent group, is shown in Figure 3A. After 2 years of follow-up, survival in patients with AS tended to be slightly worse than expected, but this did not reach statistical significance. However, when this comparison was repeated, this time censoring only for surgery but not for the development of symptoms, survival was significantly worse than that in the referent group (Figure 3B).

Discussion

In this study of 622 patients with asymptomatic AS and a peak velocity by Doppler echocardiography of at least 4 m/s or greater, we obtained follow-up for an average of >5 years. The course of these patients was not benign. We noted that the likelihood of developing cardiac symptoms during this time period was high; the Kaplan-Meier probability of remaining symptom-free while unoperated was only 33% at 5 years. The probability of remaining free of cardiac events, including cardiac death or aortic valve surgery, was 80% at 1 year, 63% at 2 years, and 25% at 5 years.

In our earlier study, no patient had sudden death unpreceded by symptoms. However, in this larger population with longer follow-up, sudden death not preceded by symptoms was observed in 11 (4.1%), or 1% per year, of the 270 patients who did not undergo aortic valve replacement. Medical follow-up was limited in approximately half of these patients. These patients exhibited a broad range of ages, aortic valve velocities, and aortic valve areas. It is possible that with closer monitoring or exercise testing, patients who were no longer asymptomatic and at risk for sudden death may have been identified. Nevertheless, it appears that patients with asymptomatic, severe AS have a small but real risk of sudden death.

Independent predictors of the development of cardiac symptoms were aortic valve area and left ventricular hypertrophy. Independent predictors of all-cause mortality in the entire population followed up until surgery were age, chronic renal failure, inactivity, and aortic valve velocity. Thus, clinical characteristics and echocardiographic parameters were imperfect for identifying unoperated patients at risk of death.

Importantly, compared with an age- and sex-matched referent group, there was a trend toward increased all-cause mortality in these patients, as shown in Table 4. The table details the predictors of all-cause mortality censored at surgery, with both univariate and multivariate analyses provided.
mortality in asymptomatic patients with AS. This divergence of survival curves, which was not observed in our earlier study with a shorter follow-up,1 appeared after 2 years of follow-up.

Prior studies have considered an aortic valve Doppler velocity >4.0 m/s to indicate severe AS.10 However, as shown herein, patients with more severe obstruction (peak velocity $\geq$4.5 m/s) had a higher likelihood of developing symptoms (RR, 1.34; 95% CI, 1.04 to 1.72) as well as aortic valve replacement or death (RR, 1.48; 95% CI, 1.20 to 1.81) compared with those with less severe obstruction (peak velocity <4.5 m/s). Thus, the more severe the obstruction to outflow, the worse the outcome in this group of asymptomatic patients. In consideration of this factor, the asymptomatic patient with a peak velocity of $\geq$4.5 m/s might be considered for prophylactic aortic valve replacement. Ejection fraction did not emerge as a predictor of poor outcome. However, in this asymptomatic population, only 3% had an ejection fraction <50%.

Recent investigations have shown increased mortality in patients with mild and moderate AS12 and even in patients with aortic sclerosis.13 The risk of death in those populations was higher than that observed in our population. However, both of those studies included patients with coronary artery disease; cardiac events were increased in this subgroup. The study by Otto et al13 also included patients with cardiac symptoms. The intent of our study was to evaluate a population with isolated, asymptomatic AS. Therefore, we excluded symptomatic patients as well as patients with prior myocardial infarction or coronary revascularization.

The protective effect of aortic valve surgery was highly significant in the multivariate analysis of predictors of cardiac death and all-cause mortality. It is possible that subtle but irreversible myocardial damage may occur in asymptomatic patients and may affect long-term outcome. Not only systolic but also diastolic dysfunction may occur.14 This may be accompanied by interstitial fibrosis, which regresses only very slowly after aortic valve replacement.15 We have observed that in some patients with severe AS, moderate to severe pulmonary hypertension may develop as a consequence of valvular heart disease.16 This may contribute to increased morbidity and mortality if surgery is delayed. Improvements in surgical techniques have reduced the morbidity of aortic valve surgery to <5% at high-volume centers.17–19 This is true even in patients with left ventricular dysfunction17,18 and in the elderly.19 The perioperative mortality in our population was low (1.4%); however, it may not be possible to extrapolate these results to centers with a higher perioperative mortality.

Limitations
The study patients were identified retrospectively. Patients were included on the basis of peak aortic valve velocity; aortic valve area was not available in all patients, as it was not routine practice to determine the Doppler-derived valve area during the early period of this study. Their asymptomatic status was determined by review of medical records obtained at and before the time of the Doppler examination. Forty-three (7%) patients were inactive, living in assisted-care facilities. It is possible that with more vigorous activity, these patients would have been symptomatic. Nevertheless, we thought it important to include these patients as representative of part of the population with asymptomatic, severe AS. Follow-up information and information about patient outcome and subsequent development of symptoms were obtained prospectively and reviewed separately. Dyspnea was considered to represent a cardiac symptom, although in some patients, it may have been related to other causes. Information about statin therapy, which has recently been shown to be associated with slower progression of AS,20 possibly by inhibiting a proliferative atherosclerosis-like process in the aortic valve, was not available.21 We did not quantify the extent of aortic valve calcification, which has been shown to be associated with more rapid progression of stenosis, as reflected by the aortic valve velocity.1 The impact of aortic valve replacement on survival of the asymptomatic patient could best be assessed in a randomized trial, as it is possible that the selection of healthier patients for surgery by factors not captured in our database contributed to the independent, apparently protective effect of surgery. In our population, 90 patients developed symptoms but did not undergo surgery. The reasons for this likely included age, comorbidities, patient preference, and failure to report symptoms to the physician. Therefore, the survival of our initially asymptomatic group of patients with severe AS was significantly worse than that of a referent group when we censored at surgery but did not exclude patients who subsequently developed symptoms. Early referral to aortic valve surgery, even in the asymptomatic patient, probably would have improved survival.

Conclusion
The majority of patients with asymptomatic, hemodynamically significant AS will develop symptoms within 5 years. Aortic valve area and left ventricular hypertrophy were predictive of the development of symptoms. Predictors of all-cause mortality in the initially asymptomatic, unoperated patient were age, chronic renal failure, inactivity, and aortic valve velocity. Sudden death, unrelied by symptoms, occurs in $\approx$1% per year, and standard clinical and echocardiographic characteristics were imperfect in identifying these patients.

References
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