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Background—We sought to assess the outcome of asymptomatic patients with very severe aortic stenosis.

Methods and Results—We prospectively followed 116 consecutive asymptomatic patients (57 women; age, 67±16 years) with very severe isolated aortic stenosis defined by a peak aortic jet velocity (AV-Vel) ≥5.0 m/s (average AV-Vel, 5.37±0.35 m/s; valve area, 0.63±0.12 cm^2). During a median follow-up of 41 months (interquartile range, 26 to 63 months), 96 events occurred (indication for aortic valve replacement, 90; cardiac deaths, 6). Event-free survival was 64%, 36%, 25%, 12%, and 3% at 1, 2, 3, 4, and 6 years, respectively. AV-Vel but not aortic valve area was shown to independently affect event-free survival. Patients with an AV-Vel ≥5.5 m/s had an event-free survival of 44%, 25%, 11%, and 4% at 1, 2, 3, and 4 years, respectively, compared with 76%, 43%, 33%, and 17% for patients with an AV-Vel between 5.0 and 5.5 m/s ($P<0.0001$). Six cardiac deaths occurred in previously asymptomatic patients (sudden death, 1; congestive heart failure, 4; myocardial infarction, 1). Patients with an initial AV-Vel ≥5.5 m/s had a higher likelihood (52%) of severe symptom onset (New York Heart Association or Canadian Cardiovascular Society class >II) than those with an AV-Vel between 5.0 and 5.5 m/s (27%; $P=0.03$).

Conclusions—Despite being asymptomatic, patients with very severe aortic stenosis have a poor prognosis with a high event rate and a risk of rapid functional deterioration. Early elective valve replacement surgery should therefore be considered in these patients. (***Circulation*. 2010;121:151-156.**)

Key Words: aortic stenosis ■ risk factors ■ stenosis ■ valves

Severe symptomatic aortic stenosis is associated with a very poor outcome unless an aortic valve replacement procedure is performed.[1–3] In contrast, the prognosis of asymptomatic patients with severe aortic stenosis is rather favorable; generally, a watchful waiting approach has been demonstrated to be safe in such patients.[4–7] Such a strategy involves performing regular follow-up exams and referring patients to surgery promptly after symptom onset. Nevertheless, some patients with asymptomatic severe aortic stenosis might benefit from early elective surgery.[8] The arguments in favor of an earlier intervention include a higher operative risk for more symptomatic patients[9]; the eventual presence of latent symptoms; and the risks of late symptom reporting,[10] of death while on a waiting list for surgery,[11] of sudden death (although low in asymptomatic patients),[4,5,12–14] and of irreversible myocardial damage. On the other hand, the immediate operative risk, the long-term morbidity and mortality related to the prosthetic valve, and the potential need for reoperation have to be taken into account.[15] Elective surgery cannot be recommended in every patient with asymptomatic severe aortic stenosis, and predictors identifying high-risk patients need to be identified.[8]

Clinical Perspective on p 156

We have demonstrated that in patients with severe aortic stenosis, the presence of a calcified aortic valve, combined with rapid hemodynamic progression, identifies a high-risk population in whom early elective surgery may be considered.[5] Peak aortic jet velocity, which is a marker of disease severity, has been shown to be an important predictor of outcome with incrementally higher event rates among asymptomatic patients with mild, moderate, and severe aortic stenosis.[4,5,16] In addition, among patients with severe aortic stenosis, higher aortic jet velocities have been linked to earlier need for surgery.[14,17] Because of the paucity of available data, the current European Society of Cardiology guidelines do not issue a recommendation for patients with asymptomatic very severe aortic stenosis.[7] The American College of Cardiology/American Heart Association guidelines consider the presence of very severe aortic stenosis (defined by a peak aortic jet velocity >5.0 m/s, a mean gradient >60 mm Hg, and a valve area <0.6 cm^2) as a Class IIb indication for surgery when the expected operative mortality rate is <1%.[6] However, the outcome of patients with very severe aortic stenosis has not been assessed specifically

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so far. We therefore prospectively studied the natural history of a large cohort of consecutive patients with asymptomatic very severe aortic stenosis to assess the clinical outcome of these patients and the potential implications for the timing of surgery.

Methods

Patient Population

All patients who were examined in our outpatient clinic for valvular heart disease between 1995 and 2008 and were found to have a stenotic native aortic valve with a peak aortic jet velocity ≥5.0 m/s were included in the study. Exclusion criteria were additional hemodynamically significant valve lesions (moderate or severe) or the presence of symptoms.

According to these criteria, 116 patients (age, 67±15 years; 57 female; average aortic valve peak velocity, 5.37±0.34 m/s) were identified. Color Doppler showed additional mild aortic regurgitation in 48 patients and mild to moderate aortic regurgitation in 11 patients. Forty-eight patients had mild and 18 patients had mild to moderate mitral regurgitation; 49 patients had mild tricuspid regurgitation; and 3 patients had additional mild mitral stenosis.

Echocardiographic Data

Echocardiography was performed with commercially available ultrasound systems. All patients underwent a comprehensive examination that included M-mode, 2-dimensional echocardiography, conventional, and color Doppler by an experienced echocardiographer. Multiple transducer positions were used to record peak aortic jet velocities, and aortic valve area was calculated with the continuity equation.[18] The degree of aortic valve calcification was scored according to the following previously described criteria: 1=no calcification, 2=mild calcification (isolated, small spots), 3=moderate calcification (multiple bigger spots), and 4=heavy calcification (extensive thickening/calcification of all cusps).[5]

Follow-Up

Patients were followed up prospectively after the initial examination at the outpatient clinic for valvular heart disease. Patients were scheduled to undergo follow-up exams at 6-month intervals. The follow-up information was obtained from interviews with the patients, their relatives, and their physicians. Information about the development of cardiac symptoms, eventual aortic valve replacement, and death was obtained. Exercise testing was performed in selected patients when doubt about whether they were truly asymptomatic existed. The decision to perform an exercise test was made on an individual basis according to clinical judgment. The only criterion used to refer a patient to surgery after an exercise test was the occurrence of symptoms during exercise.

For the assessment of outcome, end points were defined as cardiac death or indication for aortic valve replacement according to the accepted guidelines (including symptom development, left ventricular dysfunction, symptoms during an exercise test, or rapid hemodynamic progression in the presence of a significantly calcified valve). The outcome of patients with very severe aortic stenosis was also compared with the outcome of 82 patients with a peak aortic jet velocity between 4.0 and 5.0 m/s from a previously reported series.[5]

Deaths were classified as noncardiac or cardiac. Cardiac deaths were classified as directly related to aortic stenosis (sudden death, congestive heart failure) or to other cardiac pathology.

Statistical Analysis

Continuous variables are described by mean±SD. Potential follow-up was quantified by the reverse Kaplan–Meier method.[19] Overall event-free survival was described by the Kaplan–Meier method, including the SE for the estimated event-free survival proportion.

The effect of potential prognostic factors (age, sex, hypercholesterolemia, diabetes mellitus, arterial hypertension, coronary artery disease, aortic valve jet velocity at entry, and degree of aortic valve calcification) on chance of event-free survival was studied by simple and multiple Cox regression models. The strength of the effect was quantified by the unadjusted and adjusted hazard ratio estimates. The assumption of proportional hazards was assessed by adding interactions of all prognostic factors to the log of time. In case of a time-dependent effect of a variable, a weighted Cox regression method was used to estimate hazard ratios.[20]

For the analysis of absolute survival, patients who had a noncardiac cause of death were censored at the moment of death. In all statistical tests, values of $P<0.05$ were considered to indicate statistical significance.

Table 1. Baseline Patient Characteristics According to Initial Peak Aortic Jet Velocity

	All Patients (n=116)	Peak Aortic Jet Velocity 5.0 to 5.5 m/s (n=72)	Peak Aortic Jet Velocity ≥5.5 m/s (n=44)
Female sex, n (%)	57 (49)	35 (49)	22 (50)
Age, y	67±15	67±15	66±15
Peak aortic jet velocity, m/s	5.37±0.35	5.15±0.14	5.72±0.28
Aortic mean gradient, mm Hg	74.5±11.2	69±8	83±11
Aortic valve area, cm^2	0.63±0.12	0.62±0.12	0.60±0.12
Indexed aortic valve area, cm^2/m^2	0.33±0.06	0.33±0.06	0.33±0.07
Coronary artery disease, n (%)	26 (22)	15 (21)	11 (25)
Hypertension, n (%)	64 (56)	37 (53)	27 (61)
Diabetes mellitus, n (%)	10 (9)	9 (13)	1 (2)
Hypercholesterolemia, n (%)	36 (32)	21 (30)	15 (34)

Results

Follow-up information was complete for 113 patients (97.4%). The baseline characteristics of the patients are given in Table 1.

Event-Free Survival

During a potential median follow-up of 41 months (interquartile range, 26 to 63 months), 96 events were observed, including indication for aortic valve replacement in 90 patients and cardiac deaths in 6 patients. Rates of event-free survival were 64±4% at 1 year, at 36±5% at 2 years, 25±4% at 3 years, 12±4% at 4 years, and 3±10% at 6 years (Figure 1).

Deaths

Of the 9 deaths that occurred in patients who did not develop criteria for surgery, 6 were of cardiac origin. One sudden death occurred in a 62-year-old asymptomatic patient. The reasons for the other 5 cardiac deaths were congestive heart failure with multiorgan failure developing in the setting of a febrile state (n=3), congestive heart failure (n=1), and myocardial infarction (n=1). All 5 patients were confirmed to be asymptomatic at the last examination performed within 6 months before death. Age was associated with cardiac death (hazard ratio, 1.11; 95% confidence interval, 1.02 to 1.23; $P=0.02$). The 3 noncardiac deaths were due to stroke, pneumonia, and pancreatic cancer. In addition, 2 patients who refused surgery despite the development of progressive

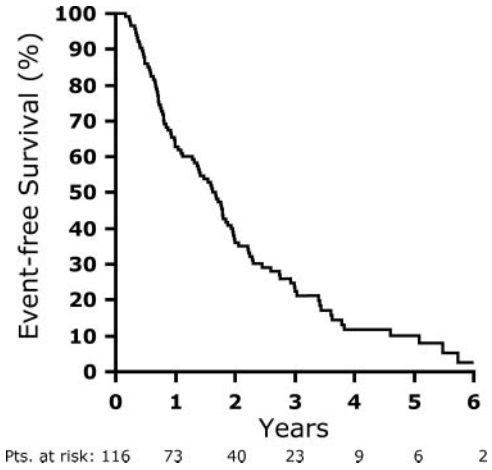

Figure 1. Kaplan–Meier event-free survival rate for the entire patient population with very severe aortic stenosis defined by a peak aortic jet velocity ≥5.0 m/s.

symptoms died of heart failure and experienced sudden death, respectively.

Indications for Aortic Valve Replacement Surgery

During follow-up, surgery was indicated in accordance with the guidelines in 90 patients for the following reasons: development of symptoms (n=73), severe aortic valve calcification and rapid hemodynamic progression (n=10), positive exercise test (n=4), and reduced left ventricular function (n=2). One asymptomatic patient was electively operated before major noncardiac surgery.

Surgery

Seventy-nine patients underwent aortic valve replacement. Ten patients refused surgery. One patient is currently awaiting surgery. Fifty-five patients received a biological valve prosthesis, 19 received a mechanical valve prosthesis, and 5 had a Ross procedure. Fourteen patients underwent concomitant aortocoronary bypass surgery.

In total, 8 of the patients who had undergone surgery died during the follow-up period. There was 1 perioperative death. Five deaths occurred in the early postoperative period (1 to 3 months after surgery): cardiac failure (n=2), myocardial infarction and multiorgan failure (n=1), aspiration pneumonia (n=1), and unknown (n=1). There were 3 late postoperative deaths: prosthetic valve endocarditis and candida septicemia (n=1), heart failure (n=1), and unknown (n=1).

Potential Prognostic Factors

Peak aortic jet velocity affected event-free survival rate among patients with severe aortic stenosis. Event-free survival rates for patients with severe aortic stenosis defined by a peak aortic jet velocity between 4.0 and 5.0 m/s (n=82) were 82±4% at 1 year, 70±5% at 2 years, 49±6% at 3 years, and 39±16% at 4 years. Event-free survival rates were significantly worse for patients with very severe aortic stenosis defined by a peak aortic jet velocity between 5.0 and 5.5 m/s (n=72): 76±5% at 1 year, 43±6% at 2 years, 33±6% at 3 years, and 17±5% at 4 years. Event-free survival rates were even worse for patients with a peak aortic jet

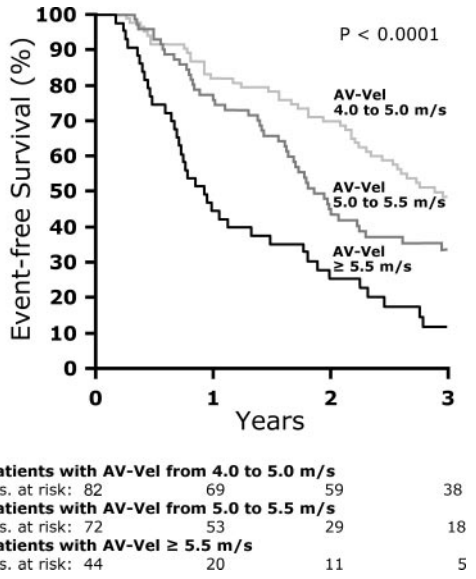

Figure 2. Kaplan–Meier event-free survival rate for patients with a peak aortic jet velocity (AV-Vel) between 4.0 and 5.0 m/s (light gray line; n=82) vs between 5.0 and 5.5 m/s (dark gray line; n=72) vs ≥5.5 m/s (black line; n=44).

velocity ≥5.5 m/s (n=44) with 44±8% at 1 year, 25±7% at 2 years, 11±5% at 3 years, and 4±4% at 4 years ($P<0.0001$; Figure 2). Furthermore, patients with higher aortic jet velocities had a more pronounced symptom onset; in the group of patients with an initial aortic jet velocity ≥5.5 m/s, 52% of the patients presented with moderate to severe symptoms (New York Heart Association or Canadian Cardiovascular Society class >II), compared with 27% of patients with a peak aortic jet velocity between 5.0 and 5.5 m/s ($P=0.03$). Thus, patients with a peak aortic jet velocity ≥5.5 m/s had a more severe symptom onset in addition to a shorter time to symptom development.

For the entire patient population, aortic valve area was 0.62±0.12 cm^2, and valve area indexed to body surface area was 0.33±0.06 cm^2/m^2. Valve area did not provide additional prognostic information in this high-risk group. The outcome of patients with an aortic valve area <0.6 cm^2 was not significantly different from the outcome of those with a valve area ≥0.6 cm^2 ($P=0.12$; Figure 3). Valve areas were not statistically significantly different between patients presenting with a peak aortic jet velocity between 5.0 and 5.5 m/s and those with a peak aortic jet velocity ≥5.5 m/s (0.63±0.12 versus 0.60±0.12 cm^2; $P=0.23$).

All but 7 patients had moderately to severely calcified aortic valves and valve calcification was not associated with event-free survival.

Because of an observed time-dependent effect of diabetes mellitus, its hazard ratio was obtained by means of weighted rather than standard Cox regression.[20] No time-dependent effects were observed for the other prognostic factors. Age, sex, significant coronary artery disease, hypercholesterolemia, and arterial hypertension were not found to be associated with event-free survival (Table 2). Coronary artery disease was present in 26 patients (22%). The incidence of coronary artery disease was comparable to that of our

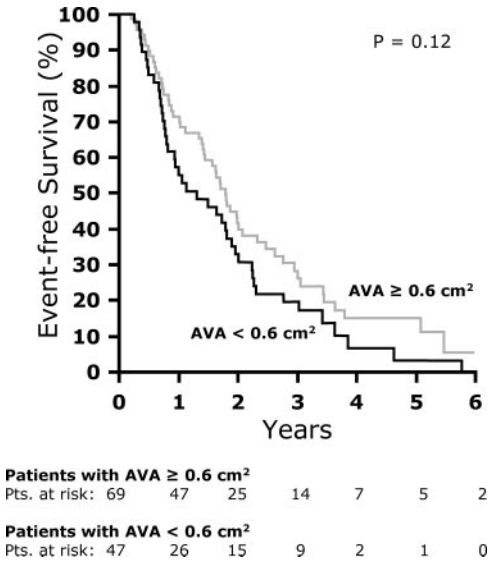

Figure 3. Kaplan–Meier event-free survival rate for patients with an aortic valve area (AVA) ≥0.6 cm^2 (gray line; n=69) vs <0.6 cm^2 (black line; n=47).

previous study (26%). We have demonstrated previously that patients with aortic stenosis and coronary artery disease have a poorer chance of event-free survival and a more rapid hemodynamic progression.[5,16] Because of a generally poor event-free survival rate among patients with very severe aortic stenosis, the presence of coronary artery disease was not of additional prognostic importance in this patient group. Treatment with a statin (n=28), a renin-angiotensin-aldosterone system inhibitor (n=46), or a β-blocker (n=16) did not affect event-free survival rate.

Discussion

Calcific aortic valve disease encompasses a broad disease spectrum ranging from aortic sclerosis without hemodynamic obstruction to severe aortic stenosis. This is the first study to specifically assess outcome in a subset of patients with very severe aortic stenosis, thereby showing that aortic jet velocities permit risk stratification even beyond the conventional definition of severe aortic stenosis.

The discussion of the optimal timing of valve replacement in patients with aortic stenosis is evolving. It has long been recognized that symptomatic patients with severe stenosis need to undergo surgery rapidly.[2] Although a watchful waiting approach is generally justified in asymptomatic patients with severe stenosis, there are nevertheless concerns when such a strategy is followed.[5] Among them are the risks of irreversible myocardial damage, sudden cardiac death, delayed symptom reporting, and dying while on a waiting list. Because improved surgical techniques have led to lower operative mortality and morbidity rates, the issue of lowering the threshold of when to refer a patient to surgery is currently discussed. Given that long asymptomatic disease courses have been reported and given the immediate risks of surgery and potential long-term complications after valve replacement, early elective surgery cannot be uniformly recommended in asymptomatic patients with aortic stenosis.

It has recently been demonstrated that risk stratification is helpful in such patients and that high-risk patients such as those with significantly calcified valves and a rapid hemodynamic progression[5] or those with a positive exercise test[21] (the most important criterion being exercise-induced symptoms[22]) are likely to benefit from early elective surgery, which is now an accepted surgical indication in both the American College of Cardiology/American Heart Association and the European Society of Cardiology recommendations. The role of B-type natriuretic peptide is still under investigation; although low values indicate a good prognosis, cutoff levels for an unfavorable outcome need to be defined.[23,24]

Many clinicians follow patients with very severe aortic stenosis conservatively as long as they are asymptomatic. Because of a lack of data describing the outcome of these patients, elective surgery was not recommendable so far in asymptomatic patients on the grounds of the presence of a very severe stenosis.

Otto and colleagues[4] have shown that peak aortic jet velocity is an important predictor of outcome in patients with

Table 2. Event-Free Survival: Univariate and Multivariate Analyses of Clinical and Echocardiographic Explanatory Variables

	Univariate Analysis		Multivariate Analysis	
Variable	*P*	HR (95% CI)	*P*	HR (95% CI)
Age >70 y	0.93	1.02 (0.68–1.54)	0.88	1.04 (0.66–1.62)
Female sex	0.43	1.17 (0.78–1.76)	0.57	1.14 (0.72–1.81)
Coronary artery disease	0.87	1.04 (0.64–1.64)	0.80	0.94 (0.55–1.55)
Hypertension	0.87	0.97 (0.65–1.45)	0.16	0.70 (0.43–1.15)
Diabetes mellitus*	0.016	1.47 (1.07–2.02)	0.0025	1.84 (1.24–2.73)
Hypercholesterolemia	0.14	1.39 (0.89–2.13)	0.043	1.68 (1.02–2.75)
Aortic valve area <0.6 cm^2	0.12	1.38 (0.92–2.07)	0.36	1.25 (0.77–2.02)
Aortic valve peak velocity ≥5.5 m/s	0.001	2.0 (1.31–3.03)	0.0069	1.88 (1.19–2.96)

HR indicates hazard ratio; CI, confidence interval.

*Because a time-dependent effect of diabetes mellitus was observed after testing interactions with the log of time (univariate, *P*=0.023; multivariate, *P*=0.030), HRs obtained by a weighted Cox regression analysis are provided for this variable.[20]

a broad range of disease severity, with an increasingly worse outcome for patients with mild (peak aortic jet velocity <3 m/s), moderate (peak aortic jet velocity 3 to 4 m/s), and severe (peak aortic jet velocity ≥4 m/s) stenosis. Recently, Monin and colleagues[17] have proposed a risk score model in which increasing peak aortic jet velocities and B-type natriuretic peptide levels were predictive of outcome in patients with aortic jet velocities ≥3.0 m/s. Previously, Pellikka et al[14] have described a significantly worse outcome for patients with a peak aortic jet velocity ≥4.5 m/s with a relative risk for cardiac events (aortic valve surgery or death) of 1.48. We have shown that rapid hemodynamic progression in patients with already severe stenosis is associated with poor outcome.[5]

This is the first study to specifically assess the outcome of a relatively large group of asymptomatic patients with very severe aortic stenosis defined by a peak aortic jet velocity ≥5 m/s. The present study shows that patients with very severe aortic stenosis have a very poor event-free survival rate. Strikingly, a 62-year-old patient died suddenly, and 4 previously asymptomatic patients with preserved ventricular function died of congestive heart failure. In 3 of the 4 patients, a febrile state triggered the events. These data seem to indicate that very severe aortic stenosis carries an increased risk of rapid clinical deterioration and an impaired reserve of adaptation to hemodynamic stress.

The subgroup of patients with a peak aortic jet velocity ≥5.5 m/s had an even worse event-free survival rate and presented with more severe symptoms compared with patients with a peak aortic jet velocity between 5.0 and 5.5 m/s. Peak aortic jet velocity thus yields important prognostic information in the group of patients with severe aortic stenosis. Because of the high event rate and the possibility of rapid deterioration, considering early elective surgery in patients with very severe aortic stenosis might be worthwhile even when they are still asymptomatic.

The evidence for performing elective surgery is strongest in the subgroup with a peak aortic jet velocity ≥5.5 m/s, judging from the high event rate that was documented in this patient group. However, the event rate is also high at a threshold of 5.0 m/s. This study also shows that symptom onset is more severe with a peak aortic jet velocity ≥5.5 m/s and that 4 of the 6 cardiac deaths were documented in patients with aortic jet velocities between 5.0 and 5.5 m/s. These data support the concept of elective surgery in patients who present with an aortic jet velocity ≥5.0 m/s.

Surprisingly, aortic valve area did not affect the outcome of patients with very severe aortic stenosis defined by a peak aortic jet velocity of ≥5.0 m/s, although aortic valve areas encompassed a broad range of values (from 0.35 to 0.91 cm^2). This may be explained by technical limitations of determining valve area by the continuity equation in clinical practice. Thus, in the setting of severe aortic stenosis with a valve area of ≤1 cm^2, the actual hemodynamic load on the left ventricle may be reflected more accurately by transaortic gradients and flow velocities than by valve area.

A relatively large variability of aortic valve area measurements for a given peak aortic jet velocity has also been confirmed recently by Minners and colleagues.[25] Although discrepancies between valve area and aortic jet velocity measurements may be more difficult to interpret in the setting of a paradoxical low flow aortic stenosis,[26] all the patients in our study fulfilled the criteria of severe stenosis in terms of both valve area and peak velocity.

Clinical factors did not have additional explanatory power in this group of patients with very severe aortic stenosis, a fact that might be explained by a very high overall event rate. It is of note that most patients with very severe aortic stenosis defined by a peak aortic jet velocity ≥5.0 m/s have extensively calcified valves. Indeed, a correlation between stenosis severity and aortic valve calcification has been described. Hence, it is not unsurprising that aortic valve calcification does not have additional explanatory power in patients with very severe stenosis. However, in patients with a broader range of stenosis severity, including patients with less severe disease, calcification of the aortic valve is associated with fast hemodynamic progression and poor chance of event-free survival.[5,16,27]

Study Limitations

It might be viewed as a limitation that 10 patients with calcified aortic valves and rapid hemodynamic progression were referred to surgery despite being asymptomatic, although this is an accepted indication for surgery according to current guidelines.[6,7] In a separate analysis in which these patients were censored when the indication for surgery was reached, similar results were observed; event-free survival rates for patients with a peak aortic jet velocity between 5.0 and 5.5 m/s were 81±5% at 1 year, 48±6% at 2 years, 37±6% at 3 years, and 21±6% at 4 years, compared with 49±8% at 1 year, 32±8% at 2 years, 15±6% at 3 years, and 7±6% at 4 years for patients with a peak aortic jet velocity ≥5.5 m/s ($P=0.006$). The study was not designed to assess and compare surgical risks and is limited in this regard by the number of patients undergoing surgery.

Conclusions

Despite being asymptomatic, patients with very severe aortic stenosis have a poor prognosis with a high event rate and a risk of rapid functional deterioration. Therefore, early elective valve replacement surgery should be considered in these patients.

Disclosures

None.

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CLINICAL PERSPECTIVE

This is the first study to assess the outcome of a large series of asymptomatic patients with very severe aortic stenosis managed according to current guidelines. One hundred sixteen consecutive asymptomatic patients with isolated very severe aortic stenosis defined by a peak aortic jet velocity ≥5.0 m/s were prospectively followed up for a median of 61 months. Event-free survival rate (indication for surgery, 90; cardiac death, 6) was poor for patients with a peak aortic jet velocity between 5.0 and 5.5 m/s (n=72), with 76±5% at 1 year, 43±6% at 2 years, 33±6% at 3 years, and 17±5% at 4 years; it was even worse for patients with a peak aortic jet velocity ≥5.5 m/s (n=44), with 44±8% at 1 year, 25±7% at 2 years, 11±5% at 3 years, and 4±4% at 4 years ($P<0.0001$). In comparison, event-free survival rate for a series of 82 patients with severe aortic stenosis defined by a peak aortic jet velocity between 4.0 and 5.0 m/s was 82±4% at 1 year, 70±5% at 2 years, 49±6% at 3 years, and 39±16% at 4 years. Furthermore, 6 cardiac deaths occurred in previously asymptomatic patients with very severe aortic stenosis, and symptom onset was more severe for patients with higher peak aortic jet velocities. Peak aortic jet velocity thus yields important prognostic information in the group of patients with severe aortic stenosis. Because of the high event rate and the possibility of rapid deterioration, considering early elective surgery might be worthwhile in patients with very severe aortic stenosis even when they are still asymptomatic.