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Asymptomatic Severe Aortic Stenosis in the Elderly

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ABSTRACT

OBJECTIVES This study sought to assess the natural history and optimal timing of surgery in elderly patients with severe asymptomatic aortic stenosis (AS).

BACKGROUND AS is increasingly diagnosed in an aging population, and large numbers of elderly patients are undergoing aortic valve procedures. However, the average age of patients represented in most natural history studies on AS is between 60 and 70 years.

METHODS A total of 103 consecutive patients >70 years of age (51 female; mean age 77 ± 5 years) with asymptomatic severe AS (peak aortic jet velocity [AV-Vel] 4.7 ± 0.6 m/s) were prospectively followed.

RESULTS During follow-up, 91 events occurred, including an indication for aortic valve replacement in 82 patients and cardiac deaths in 9, respectively. Event-free survival was 73%, 43%, 23%, and 16% at 1, 2, 3, and 4 years, respectively. Physical mobility was impaired in 29% of the patients, and symptom onset was severe (New York Heart Association functional class ≥III) in 43% of those who developed symptoms. Patients with AV-Vel ≥5.0 m/s had event-free survival rates of 21% and 6% at 2 and 4 years, respectively, compared with 57% and 23% for patients with AV-Vel <5.0 m/s ($p < 0.001$). Seventy-one patients underwent aortic valve replacement, and post-operative survival was 89% and 77% after 1 and 3 years, respectively.

CONCLUSIONS In elderly patients with severe but asymptomatic AS, mild symptoms may be difficult to detect, particularly when mobility is impaired and severe symptom onset is common, warranting close clinical follow-up. Furthermore, a very high event rate can be expected, and cardiac deaths are not infrequent. Thus, elective aortic valve procedures may be considered in selected elderly patients at low procedural risk. (J Am Coll Cardiol Img 2017;10:43–50)

Calcific aortic stenosis (AS) is very common in elderly patients, who represent a growing proportion of the population in developed countries (1). The outcome of symptomatic severe AS is dismal at any age (2). Aortic valve replacement (AVR) in symptomatic severe AS is associated with improved life expectancy and quality of life in younger but also in elderly patients (3).

Due to the high prevalence of AS and easy access to echocardiography, severe AS is increasingly diagnosed in asymptomatic patients. Because of the risk of late symptom reporting and the higher surgical risk for patients with advanced symptoms, recent guidelines (4,5) recommend considering elective surgery in asymptomatic patients at high risk for developing symptoms in the near future, such as those with very severe AS (6) and those with rapid hemodynamic progression in the presence of a calcified valve (7). The proper assessment and the objectivation of the symptomatic status can be particularly challenging in elderly patients, who frequently have impaired physical mobility (8). The decision-making process regarding the management strategy, and particularly the choice between a watchful waiting strategy and

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ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis

AVR = aortic valve replacement

AV-Vel = peak aortic jet velocity

CAD = coronary artery disease

CCS = Canadian Cardiovascular Society

CI = confidence interval

HVC = heart valve clinic

NT-proBNP = N-terminal pro-B-type natriuretic peptide

NYHA = New York Heart Association

TAVR = transcatheter aortic valve implantation

surgery, involves a careful individualized risk-to-benefit assessment (9). Age-specific considerations, such as operative risk (10) and the natural history of the disease, need to be integrated. However, evidence on the natural history of severe asymptomatic AS in the elderly is lacking because it has been studied in series that included predominantly patients <70 years of age (6,7,11–16). Indeed, undertreatment of AS is particularly common in elderly patients (17).

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We therefore studied the natural history of a large cohort of consecutive elderly patients >70 years of age with asymptomatic severe AS to assess the clinical outcome of these patients and the potential implications for their management and the timing of surgery.

METHODS

STUDY POPULATION. Consecutive patients >70 years of age who were studied in our outpatient clinic for valvular heart disease between 1999 and 2009 and were found to have a stenotic native aortic valve with a peak aortic jet velocity (AV-Vel) ≥4.0 m/s were included in the study when they had no additional hemodynamically significant valve lesion (moderate to severe or severe), a normal ejection fraction (≥55%), presented without symptoms, and had no history of previous cardiac surgery.

According to these criteria, 103 patients (age 77.3 ± 4.8 years; 51 female; average AV-Vel 4.75 ± 0.57 m/s) were identified. The majority of these patients were referred from outpatient care specialists in internal medicine and general cardiologists. To compare event-free survival in younger patients, a subset of 83 consecutive patients <70 years of age with asymptomatic severe AS from an earlier series (mean age 50 ± 16 years; average AV-Vel 4.7 ± 0.6 m/s) was used (7).

CLINICAL DATA. At baseline, the following data were collected: age, sex, medications, history of hypercholesterolemia (cholesterol >200 mg/dl or patient receiving lipid-lowering therapy at baseline), diabetes mellitus, arterial hypertension (use of antihypertensive medication or average blood pressure >140/90 mm Hg based on repeated measurements), and coronary artery disease (CAD) (history of myocardial infarction, angioplasty, or angiographically documented coronary artery stenosis). The patient's mobility was evaluated in the direct interview with the patient during clinical assessment. Coronary angiography was performed in all 71 patients who underwent AVR. In addition, CAD had been documented in 5 of 32 patients who did not undergo AVR. Each patient's logistic EuroSCORE and EuroSCORE II were calculated at baseline.

ECHOCARDIOGRAPHY. Echocardiographic data were obtained using commercially available ultrasound systems. All patients underwent a comprehensive examination conducted by an experienced echocardiographer. For calculation of ejection fraction (by the Simpson biplane formula), apical 4-chamber and 2-chamber views were used. Aortic jet velocities were measured by continuous-wave Doppler using multiple imaging windows, including the apical 3- and 5-chamber, right parasternal, and suprasternal windows, and recording the highest velocity signal. Pressure gradients were estimated using the Bernoulli equation, and aortic valve area was calculated with the continuity equation. The degree of aortic valve calcification was scored according to criteria previously described (7).

FOLLOW-UP. Patients were followed up prospectively after inclusion in a heart valve clinic (HVC) program and were scheduled for 6-monthly clinical and echocardiographic re-evaluation until criteria for surgery were reached. Patients who underwent surgery had a post-operative follow-up visit in the HVC to assess the surgical outcome. Further follow-up examinations in the HVC were scheduled at extended intervals, depending on individual surgical and clinical outcomes. For the completion of post-operative follow-up data, additional follow-up information was obtained from interviews with the patients, their relatives, their physicians, and from the review of medical records. Particular care was taken to obtain information regarding the development of cardiac symptoms, eventual AVR, and death. For the assessment of event-free survival, endpoints were defined as cardiac death (directly related to AS or other cardiac pathology) or indication for AVR according to the prevailing practice guidelines. The decision to perform an exercise test was made on an individual basis according to clinical judgment. Criteria used as surgical indications included the occurrence of symptoms or an abnormal blood pressure response with exercise, but not ST-segment depression, given its limited specificity (18). Reasons for death were determined based on discussion with the primary care physician, review of medical records, or review of medical records that included autopsy records.

STATISTICAL ANALYSIS. Quantitative data are expressed as mean ± SD. Event-free survival was determined with the Kaplan-Meier method, and

survival estimates as well as 95% confidence interval (CI) are reported.

The magnitude of the effect of different variables (age, sex, hypercholesterolemia, diabetes mellitus, arterial hypertension, CAD, and aortic valve jet velocity) at baseline is graphically represented by Kaplan-Meier survival functions. The effect of these variables was analyzed by simple (for marginal effects) and multiple (for partial effects) Cox regression models using the Wald test. Values of $p < 0.05$ were considered to indicate statistical significance.

Overall survival as determined at the last follow-up (taking into account perioperative deaths and postoperative follow-up for those patients who required surgery) was also analyzed and compared with the survival of age- and sex-matched control subjects. These data were taken from the 2012 Austrian life tables, which were provided by the Austrian Statistical Office and represent the survival of the general Austrian population. Statistical analyses were performed using SAS version 9.2 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Follow-up information was complete for 96 patients (93.2%). Two patients were lost to follow-up while they were still asymptomatic and 5 patients after AVR had been performed. The baseline characteristics of the patients are given in Table 1. All patients had "classical" severe AS (AV-Vel 4.7 ± 0.6 m/s; aortic valve area 0.7 ± 0.2 cm^2). As noted by color Doppler, additional mild aortic regurgitation was present in 55 patients. Sixty-five patients had mild mitral regurgitation, 51 had mild tricuspid regurgitation, and 2 had additional mild mitral stenosis.

TABLE 1 Baseline Patient Characteristics

	All Patients (N = 103)	Patients <80 Years of Age (n = 69)	Patients ≥80 Years of Age (n = 34)	p Value
Female	51 (50)	29 (22)	22 (65)	0.03
Age, yrs	77.3 ± 4.8	74.6 ± 3.0	82.6 ± 3.0	<0.001
Peak aortic jet velocity, m/s	4.7 ± 0.6	4.8 ± 0.6	4.7 ± 0.5	0.56
Aortic mean gradient, mm Hg	58 ± 17	58 ± 17	58 ± 17	0.98
Aortic valve area, cm^2	0.7 ± 0.2	0.7 ± 0.2	0.7 ± 0.2	0.17
Tricuspid annular plane systolic excursion, mm	24.0 ± 2.5	24.0 ± 0.7	23.0 ± 1.4	0.32
Left ventricular ejection fraction, %	61.0 ± 5.9	60.0 ± 1.3	63.0 ± 2.0	0.23
Pulmonary artery systolic pressure, mm Hg	39.2 ± 9.7	38.0 ± 10.1	41.2 ± 8.9	0.18
Interventricular septal thickness, cm	1.6 ± 0.3	1.6 ± 0.4	1.6 ± 0.6	0.50
Coronary artery disease	31 (30)	21 (30)	10 (29)	0.92
Hypertension	79 (77)	53 (77)	26 (76)	0.97
Diabetes mellitus	19 (18)	10 (14)	9 (26)	0.15
Hypercholesterolemia	40 (39)	26 (38)	14 (41)	0.73
Chronic obstructive pulmonary disease	9 (9)	6 (9)	3 (9)	0.98
Atrial fibrillation	7 (7)	4 (6)	3 (9)	0.74
Peripheral artery disease	12 (12)	7 (10)	5 (15)	0.50
Baseline logistic EuroSCORE, %	7.2 ± 4.1	5.5 ± 0.4	10.4 ± 0.7	<0.001
Beta-blocker	26 (25)	16 (23)	10 (29)	0.50
Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker	59 (57)	39 (57)	20 (59)	0.82
Statin	33 (32)	21 (30)	12 (35)	0.62
Acetylsalicylic acid	49 (48)	32 (46)	17 (50)	0.73
Thiazide diuretic	19 (18)	14 (20)	5 (15)	0.005
Loop diuretic	13 (13)	6 (9)	7 (21)	0.10
Aldosterone antagonist	2 (0.2)	2 (3)	0 (0)	0.20

Values are n (%) or mean ± SD.

COMORBIDITIES. Medical comorbidities are listed in Table 1. At baseline, the logistic EuroSCORE and the EuroSCORE II for the entire patient population were 7.2 ± 4.1% and 2.7 ± 1.9%, respectively.

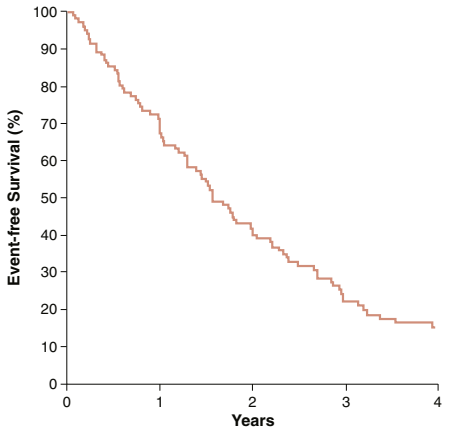
Thirty patients (29%) presented with conditions leading to restricted physical mobility. The reasons included osteoporosis or degenerative spinal disease (n = 10), arthrosis (n = 8), history of trauma (n = 3), severe chronic obstructive pulmonary disease (n = 3), idiopathic arthralgias (n = 2), peripheral artery disease (n = 2), rheumatoid arthritis (n = 1), and history of stroke (n = 1).

EVENT-FREE SURVIVAL. During a median potential follow-up of 19.4 months (interquartile range: 9.8 to 36.4 months), 91 events were observed, consisting of an indication for AVR in 82 patients and cardiac death in 9 patients. Event-free survival was 73% (95% CI: 63% to 80%) at 1 year, 43% (95% CI: 34% to 53%) at 2 years, 23% (95% CI: 16% to 33%) at 3 years, and 16% (95% CI: 10% to 25%) at 4 years (Figure 1).

INDICATIONS FOR AVR. During follow-up, surgery was indicated in 82 patients for development of symptoms (n = 76), severe aortic valve calcification and rapid hemodynamic progression (n = 3), reduced left ventricular ejection fraction (n = 2) prior to major noncardiac surgery in an asymptomatic patient (n = 1). Severe symptom onset (New York Heart Association [NYHA] functional class or Canadian Cardiovascular Society [CCS] class ≥III) was observed in 32 patients, corresponding to 43% of patients who developed symptoms during follow-up. These patients had clinical and echocardiographic characteristics that were comparable to those with mild symptom onset.

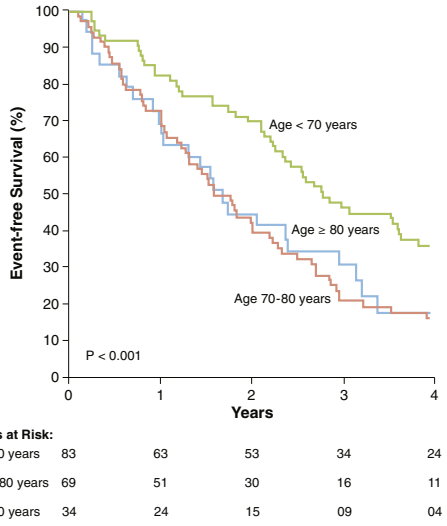
PREDICTORS OF EVENT-FREE SURVIVAL. By univariate analysis, no significant differences in event-free survival were found for sex (p = 0.87), presence of hypertension (p = 0.45), hypercholesterolemia

FIGURE 1 Event-Free Survival for the Entire Patient Population



Kaplan-Meier event-free survival for the entire patient population.

FIGURE 2 Event-Free Survival According to Age



Kaplan-Meier event-free survival for patients 70 to 80 years of age **(pink line)**, patients ≥80 years **(blue line)**, and patients <70 years **(green line)**.

(p = 0.95), or diabetes (p = 0.39). Event-free survival was not significantly different for patients between 70 and 80 years of age and patients >80 years of age (p = 0.84). In comparison, patients <70 years of age from an earlier series (mean age 50 ± 16 years, average AV-Vel 4.7 ± 0.6 m/s) had significantly lower event rates of 82% (95% CI: 72% to 90%), 70% (95% CI: 59% to 80%), 46% (95% CI: 35% to 57%), and 37% (95% CI: 27% and 49%) at 1, 2, 3, and 4 years, respectively (p < 0.001) (**Figure 2**) (7).

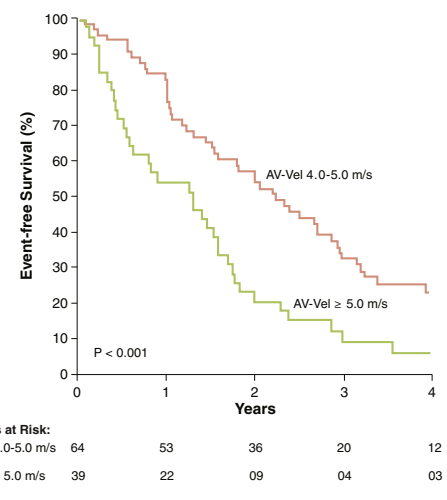
AV-Vel was a strong prognostic factor in elderly patients with severe asymptomatic AS. Event-free survival for patients with AV-Vel between 4.0 and 5.0 m/s (n = 64) was 84% (95% CI: 73% to 91%) at 1 year, 57% (95% CI: 44% to 68%) at 2 years, 32% (95% CI: 21% to 44%) at 3 years, and 23% (95% CI: 14% to 35%) at 4 years compared with 54% (95% CI: 38% to 69%) at 1 year, 21% (95% CI: 11% to 36%) at 2 years, 9% (95% CI: 3% to 24%) at 3 years, and 6% (95% CI: 2% to 21%) at 4 years for patients with AV-Vel ≥5 m/s (n = 39; p < 0.001) (**Figure 3**).

All patients had moderately (n = 89) or severely (n = 14) calcified aortic valves. Event-free survival was comparable for patients with moderate and with severe valve calcification (p = 0.11).

Patients with concomitant CAD had significantly higher event rates. Event-free survival rates were 68% (95% CI: 50% to 82%) at 1 year, 19% (95% CI: 9% to 37%) at 2 years, 13% (95% CI: 5% to 30%) at 3 years, and 6% (95% CI: 2% to 22%) at 4 years, respectively, for patients with CAD compared with 75% (95% CI: 63% to 83%) at 1 year, 53% (95% CI: 41% to 64%) at 2 years, 28% (95% CI: 18% to 40%) at 3 years, and 21% (95% CI: 13% to 33%) at 4 years, respectively, for patients without CAD (p = 0.008).

By multivariate analysis, presence of CAD (p = 0.004) and AV-Vel at baseline (p = 0.01) were the

FIGURE 3 Event-Free Survival According to AV-Vel



Kaplan-Meier event-free survival for patients with an AV-Vel of 4.0 to 5.0 m/s **(pink line)** and patients with an AV-Vel ≥5 m/s **(green line)**. AV-Vel = peak aortic jet velocity.

only independent predictors of event-free survival (Table 2).

SURGERY. Seventy-one of the patients with an indication for surgery underwent conventional AVR, whereas 11 patients refused surgery (7 of 69 patients 70 to 80 years of age and 4 of 34 patients >80 years of age; p = 0.80). All patients underwent valve replacement with a bioprosthetic valve, and 16 patients underwent concomitant aortocoronary bypass surgery.

Twenty-one of the patients who underwent surgery died during the follow-up period. Five perioperative deaths (within 30 days of surgery) occurred because of aortic dissection in 1, pneumonia in 3, and systemic inflammatory response syndrome in 1.

Two patients died in the early post-operative period (1 to 3 months after surgery) of myocardial infarction in 1 and bilateral pneumonia in 1. The reasons for 14 late post-operative deaths were unknown in 2, prosthetic valve endocarditis in 1, decompensated heart failure in 5, myocardial infarction in 1, mediastinal carcinoma in 1, metastatic colorectal cancer in 1, trauma in 2, and pulmonary embolism in 1. Post-operative survival rates were 89% (95% CI: 79% to 94%), 81% (95% CI: 69% to 89%), 77% (95% CI: 64% to 86%), and 69% (95% CI: 55% to 80%) at 1, 2, 3, and 4 years, respectively. Severe symptom onset (NYHA functional class or CCS class ≥III, n = 29) was associated with post-operative all-cause mortality with survival rates of 95% (95% CI: 83% to 99%) at 1 year and 88% (95% CI: 72% to 96%) at 2, 3, and 4 years, respectively, for patients with mild symptom onset compared to 82% (95% CI: 64% to 93%) at 1 year, 74% (95% CI: 54% to 87%) at 2 years, 65% (95% CI: 44% to 81%) at 3 years, and 46% (95% CI: 26% to 68%) at 4 years, respectively, for those with severe symptom onset (p = 0.002) (Figure 4).

OVERALL SURVIVAL. The actuarial probability of survival at the end of the study (including deaths during conservative management, and perioperative and late deaths after aortic valve surgery) was 96% at 1 year, 92% at 2 years, 82% at 3 years, and 76% at 4 years. Mortality rates were higher for patients >80 years of age (p = 0.03). Survival rates were comparable to those predicted for age- and sex-matched control subjects of Austria's general population for the subgroups of patients between 70 and 80 years of age and those >80 years of age (p = 0.45) (Figure 5).

Fifteen deaths occurred in patients who had not developed criteria for surgery. Nine of these deaths were of cardiac origin: myocardial infarction in 2, cardiac decompensation in 5, and pneumonia leading to cardiac decompensation and subsequent multiorgan failure in 2. CAD was not previously documented in these patients. All of these 9 patients claimed to be asymptomatic at the last examination, which had been performed within 190 ± 153 days before death, and they were older than patients who did not die before obvious symptoms were detected (80.3 ± 1.6 years vs. 77.0 ± 0.5 years; p = 0.04). However, 4 of these 9 patients had exercise-limiting comorbidities that may have made the detection of mild symptoms difficult. The causes of the 6 noncardiac deaths were trauma in 2, stroke in 2, pancreatic cancer in 1, and unknown in 1.

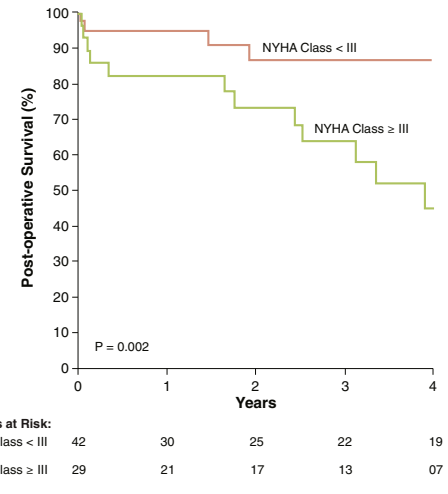
In addition, 8 of 11 patients who had refused surgery despite the development of progressive symptoms died of sudden death (n = 1), sepsis (n = 1), cardiac decompensation (n = 5), and myocardial infarction (n = 1).

TABLE 2 Event-Free Survival: Univariate and Multivariate Analysis of Potential Clinical and Echocardiographic Predictors

	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Peak aortic jet velocity ≥5 m/s	2.01 (1.37–2.95)	<0.001	1.93 (1.16–3.23)	0.01
Aortic valve area	0.28 (0.08–0.95)	0.04	1.08 (0.24–4.92)	0.92
Age	1.00 (0.95–1.05)	0.99	0.98 (0.92–1.03)	0.35
Aortic valve calcification	1.74 (0.88–3.46)	0.11	1.10 (0.54–2.24)	0.80
Hypertension	0.83 (0.52–1.34)	0.45	0.71 (0.4–1.27)	0.25
Hypercholesterolemia	1.01 (0.66–1.55)	0.95	1.42 (0.85–2.37)	0.19
Diabetes	0.78 (0.45–1.36)	0.39	0.68 (0.35–1.33)	0.26
Coronary artery disease	1.82 (1.16–2.86)	0.009	2.15 (1.29–3.6)	0.004

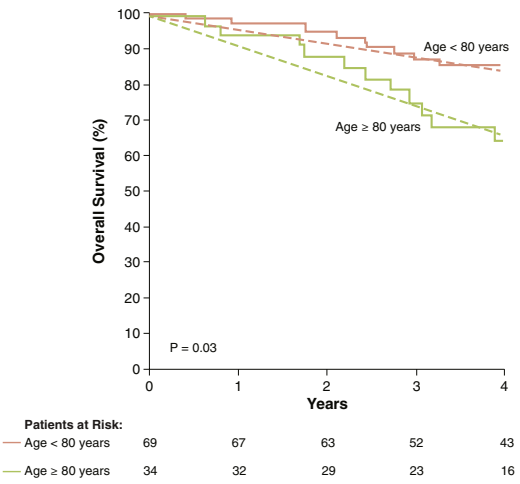
CI = confidence interval; HR = hazard ratio.

FIGURE 4 Post-Operative Survival



Kaplan-Meier post-operative survival for patients in New York Heart Association (NYHA) functional class <III **(pink line)** and patients in NYHA functional class ≥III **(green line)**.

FIGURE 5 Overall Survival



Kaplan-Meier overall survival for patients <80 years of age **(pink line)** and patients ≥80 years **(green line)** compared with the survival of age- and sex-matched control persons <80 years of age **(dashed pink line)** and persons ≥80 years **(dashed green line)**.

DISCUSSION

CHARACTERISTICS OF ELDERLY PATIENTS WITH SEVERE ASYMPTOMATIC AS. Elderly patients with asymptomatic severe AS constitute an increasingly common entity. With an increasing awareness of undertreated AS and evidence of excellent surgical outcomes (19), particularly with the advent of transcatheter aortic valve replacement (TAVR), increasing numbers of elderly patients are referred for assessment of stenotic aortic valves. The patients included in the present series had a high prevalence of conditions leading to impaired physical mobility, but otherwise they mostly did not present with important comorbidities and had a logistic EuroSCORE of 7.2 ± 4.1% and EuroSCORE II of 2.7 ± 1.9%. Thus, they constitute a low- to intermediate-risk population that is different from high-risk or inoperable symptomatic patients. Being asymptomatic, the patients in the present series did not have an indication for surgery at inclusion.

ASSESSMENT OF SYMPTOMATIC STATUS IN THE ELDERLY. Forty-three percent of the patients who developed symptoms had severe symptom onset (NYHA functional class or CCS class ≥III) despite being followed in an HVC program with 6-monthly clinical and echocardiographic follow-up examinations. It had been demonstrated previously that abrupt symptomatic deterioration increases operative mortality and that patients with advanced symptoms have a worse long-term survival (20). Such severe symptom onset in patients with impaired physical mobility may be explained by the fact that the patients cannot perform or avoid participating in activities of more than mild intensity. Symptoms that would otherwise be detected during intense or modest levels of exercise thus remain hidden. Ultimately, the symptoms become manifest at a more advanced stage with mild exertional activity. Although 29% of the patients enrolled in this series presented with obviously impaired mobility, severe symptom onset was frequently also observed in more mobile patients, indicating a high threshold for perceiving mild symptoms in elderly patients.

Early symptoms might also be concealed by the use of diuretics, which according to data from the EuroHeart survey on valvular heart disease are used in up to 62% of elderly patients with AS (17). In the present series, 30% of the patients were taking diuretic agents, most of which were thiazides prescribed at the discretion of the patient's primary care physician as antihypertensive therapy. None of these patients had a previous episode of cardiac decompensation.

Although exercise testing to unmask latent symptoms is very valuable in younger and active patients, it has a rather limited predictive value in patients >70 years of age (18). In addition, these patients frequently present with physical impairment. Nevertheless, it may be a useful test in selected elderly patients.

NATURAL HISTORY AND RISK STRATIFICATION IN ELDERLY PATIENTS WITH ASYMPTOMATIC SEVERE AS. This is the first study to specifically assess the outcome of a large cohort of elderly patients with asymptomatic severe AS. The event rate was very high in these elderly patients (mean age 77 years), with an event-free survival of only 16% at 4 years. Event rates were lower for patients <70 years of age ($p < 0.001$) but were comparable for patients in their 80s and 90s ($p = 0.84$).

AV-Vel, which has been previously shown to be of prognostic importance in asymptomatic severe AS (6,11), was also shown to be an independent predictor of outcome in the present series of elderly patients. The definition of very severe AS based on AV-Vel >5 m/s is thus of clinical relevance. Although current European Society of Cardiology guidelines define very severe AS as AV-Vel >5.5 m/s (5), we believe that based on present and previous findings (6), the adoption of a cutoff of 5.0 m/s, in analogy to the American Heart Association/American College of Cardiology guidelines (4), should be considered.

The presence of CAD was also independently associated with higher event rates and thus is concordant with previous findings in younger patients (7,21).

OUTCOME OF A WATCHFUL WAITING STRATEGY IN ELDERLY PATIENTS. The outcome of a watchful waiting strategy in elderly asymptomatic patients with severe AS is good, and survival of patients in this series was comparable to age-and sex matched subjects of the Austrian general population. Also, surgical outcomes were good, and none of the patients in our series was denied surgery at the discretion of the responsible cardiologist or cardiac surgeon. These data are in contrast to data from the EuroHeart survey, in which one-third of patients >75 years of age with an indication for aortic valve surgery was denied surgery (17). This indicates that state-of-the-art care results in excellent outcomes even in elderly patients, thus stressing the importance of treating AS patients in specialized high-volume centers with an HVC (22,23).

Nevertheless, 43% of the patients who developed symptoms had severe symptom onset (NYHA functional class or CCS class ≥III), and 9 asymptomatic patients died of cardiac causes before obvious criteria for surgery had been reached. Two of these patients died of progressive hemodynamic instability and irreversible shock in the setting of an infection, indicating a latent intolerance of enhanced circulatory demand in these elderly patients. Similar findings were previously demonstrated in patients with very severe AS (6).

ELECTIVE VALVE PROCEDURES FOR ASYMPTOMATIC ELDERLY PATIENTS. The current guidelines recommend the consideration of elective aortic valve surgery in selected asymptomatic patients at high risk for rapid onset of spontaneous symptoms if the surgical risk is low (4,5). However, the guidelines do not specifically address the large subgroup of elderly patients. Particular considerations apply to these patients and individualized risk assessment is essential (24). On a general basis, elderly patients have a higher surgical risk than younger patients, but they still may be in a low-risk category (10). Recent series report excellent outcomes for both surgery and TAVR in elderly patients (19,25). In any case, the potential morbidity associated with surgery or TAVR, including cerebrovascular events, wound infections, and prolonged recovery, must be considered. Although randomized trials are needed to compare watchful waiting with early intervention in severe asymptomatic AS and to define the role of TAVR in low- to intermediate-risk elderly patients, the present study highlights several aspects that may be of importance in this decision-making process:

1. The detection of early symptoms in elderly patients may be difficult, particularly if their physical mobility is limited.
2. Severe onset of symptoms, which is associated with worse post-operative survival, is frequent in elderly patients.
3. The event rate is very high, particularly in the group with very severe AS (defined as AV-Vel ≥5.0 m/s), in whom event-free survival was 21% and 9% at 2 and 3 years, respectively.
4. The outcome of a watchful waiting strategy appears not to be associated with excessive risk, but cardiac deaths are not infrequent even in asymptomatic elderly patients with severe AS.

Given these aspects, it may be worthwhile to consider elective valve procedures in elderly asymptomatic patients with very severe AS when their procedural risk is low.

STUDY LIMITATIONS. Although this is the first and largest study specifically addressing severe asymptomatic AS in elderly patients, the sample size was relatively small but compares well to other natural history studies of valvular heart disease.

In the 27 patients who did not have an ischemic cardiac event or undergo pre-operative coronary angiography during follow-up, the presence of subclinical CAD cannot be ruled out.

The patient's frailty or immobility was not systematically assessed by a geriatrician and thus might be subject to bias of the attending physician in the valve clinic. Bearing in mind that event-free survival mostly reflects physician judgments, it might be viewed as a limitation that the subjective assessment of the symptomatic status might be subject to inter-observer variability, and exercise testing could not be systematically performed in the elderly and often physically restricted patients included in this series. However, evidence shows that positive predictive accuracy for exercise-induced symptoms in elderly patients is limited (18).

Serum biomarkers were not routinely assessed in this patient population. At the same time, no consistent threshold of serum N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration has been defined to select patients for early elective surgery (26). In a recent study (27), an association of NT-proBNP with outcome was found in univariate analysis but not after adjustment for age, sex, and AS severity. Therefore, it was concluded that NT-proBNP should be considered cautiously in the

decision-making process of AS patients, especially in the elderly population.

CONCLUSIONS

In elderly patients with severe but asymptomatic AS, mild symptoms may be difficult to detect, particularly when their mobility is impaired and severe symptom onset is common. Furthermore, a very high event rate can be expected, and cardiac deaths are not infrequent. Thus, close clinical follow-up is warranted for all patients, and elective aortic valve procedures may be considered in selected elderly patients at low procedural risk.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Severe asymptomatic AS in elderly patients is associated with a very high event rate (including cardiac mortality), and timely symptom detection may be challenging. Close follow-up is warranted, and elective valve procedures should be considered in selected elderly patients at low procedural risk.

TRANSLATIONAL OUTLOOK: Randomized trials comparing watchful waiting with early intervention in severe asymptomatic AS are needed.

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KEY WORDS aortic stenosis, aortic valve replacement, valvular heart disease