

# Characteristics and Prognosis of Patients With Moderate Aortic Stenosis and Preserved Left Ventricular Ejection Fraction

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**Background**—Moderate aortic stenosis (MAS) has not been extensively studied and characterized, as no published study has been specifically devoted to this condition.

**Methods and Results**—We aimed to describe the characteristics of patients with MAS and to evaluate their long-term survival compared with that of the general population. This study included 508 patients (mean±SD age, 75±11 years) with MAS (aortic valve area between 1 and 1.5 cm<sup>2</sup>; mean±SD aortic valve area, 1.2±0.15 cm<sup>2</sup>) and preserved left ventricular ejection fraction. Patients were mostly (86.4%) asymptomatic or minimally symptomatic, 78.3% had hypertension, 36.2% were diabetics, and 48.3% had dyslipidemia. Each patient with MAS was matched for the average survival (per year) of all patients of the same age and same sex from our region (Somme department, north of France). During follow-up (median 47 months), 113 patients (22.2%) underwent aortic valve replacement for severe AS. The mean±SD time between inclusion and surgery was 37±22 months. During follow-up, 255 patients (50.2%) died. The 6-year survival of patients with MAS was lower than the expected survival (53±2% versus 65%). In multivariate analysis, age (hazard ratio, 1.04 [95% CI, 1.02–1.05]; *P*<0.001), prior atrial fibrillation (hazard ratio, 1.35 [95% CI, 1.05–1.73]; *P*=0.019), and Charlson comorbidity index (hazard ratio, 1.11 [95% CI, 1.05–1.18]; *P*=0.002) were associated with increased mortality. Aortic valve replacement was associated with better survival (hazard ratio, 0.38 [95% CI, 0.27–0.54]; *P*<0.001).

**Conclusions**—The results of this study show that patients with MAS present many cardiovascular risk factors, a high rate of surgery during follow-up, and increased mortality compared with the general population mainly related to associated comorbidities. Patients with MAS should, therefore, be managed for their cardiovascular risk factors and comorbidities. They require close follow-up, especially when the aortic valve area is close to 1 cm<sup>2</sup>, as aortic valve replacement performed when patients transition to severe AS and develop indications for surgery during follow-up is associated with better survival. (*J Am Heart Assoc.* 2019;8:e011036. DOI: 10.1161/JAHA.118.011036.)

**Key Words:** aortic valve replacement • aortic valve stenosis • morbidity/mortality • outcome • surgery

Aortic stenosis (AS) is the most common valvular heart disease in developed countries, and its prevalence is increasing with aging of the population.<sup>1,2</sup> Several long-term follow-up series<sup>3–5</sup> have now clearly defined the diagnosis and management of severe AS, and guidelines have now been established.<sup>6,7</sup> However, moderate AS (MAS) has not been extensively studied and clearly characterized. Although some studies focusing on mild-to-moderate AS have shown an increased incidence of cardiovascular events,<sup>8</sup> strongly influenced by comorbidities,<sup>9,10</sup> no study has been specifically

devoted to MAS. Furthermore, no data are available about the prognosis of MAS compared with the general population. The aim of this study was, therefore, to focus on MAS to describe the characteristics of this population and evaluate the long-term survival of these patients compared with that of the general population. This study included patients with a diagnosis of AS established in the echocardiography laboratories of 2 French tertiary centers (Amiens and Lille). MAS was defined as an aortic valve area (AVA) measured by echocardiography between 1 and 1.5 cm<sup>2</sup>.<sup>11</sup>

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## Clinical Perspective

### What Is New?

- Patients with moderate aortic stenosis (AS) have an increased mortality compared with the general population, mainly related to associated comorbidities.
- Cardiovascular risk factors are frequent in patients with moderate AS and must be appropriately managed.
- The cumulative incidence of aortic valve replacement at 6 years is high, reaching 30%.

### What Are the Clinical Implications?

- Patients with moderate AS should be managed for their cardiovascular risk factors.
- Patients with moderate AS and an aortic valve area close to 1 cm<sup>2</sup> should be followed up closely, as aortic valve replacement performed at the stage of severe AS in patients with an indication for surgery is associated with improved survival.

## Methods

### Inclusion and Exclusion Criteria

The data that support the findings of this study are available from the corresponding author on reasonable request. Between 2000 and 2014, patients aged  $\geq 18$  years with a diagnosis of at least mild AS (aortic valve calcification with restricted systolic leaflet motion and AVA  $< 2$  cm<sup>2</sup>) and left ventricular ejection fraction (LVEF)  $\geq 50\%$  were prospectively identified and included in an electronic database. The following patients were excluded: (1) individuals with more than mild aortic and mitral regurgitation; (2) patients with prosthetic valves, congenital heart disease (with the exception of bicuspid aortic valves), supralvalvular or subvalvular AS, or dynamic left ventricular (LV) outflow tract obstruction; and (3) individuals who declined to participate in the study. The present analysis focused on 508 patients with MAS (defined as AVA  $\leq 1.5$  and  $\geq 1$  cm<sup>2</sup>). All comorbidities were collected from medical records. The Charlson comorbidity index, comprising the sum of individual comorbidities, was calculated for each patient.<sup>12</sup> All subjects gave informed consent. This study was approved by an independent ethics committee and was conducted in accordance with institutional policies, French legislation, and the revised Declaration of Helsinki.

### Echocardiography

All patients underwent a comprehensive Doppler-echocardiographic assessment, using commercially available ultrasound systems. Aortic flow was systematically recorded using

continuous-wave Doppler on several views (apical 5 chamber, right parasternal, suprasternal, and epigastric). The view identifying the highest velocities was used to determine peak aortic jet velocity. Three consecutive measurements obtained on this view in patients in sinus rhythm and 5 consecutive measurements in patients in atrial fibrillation (AF) were systematically averaged. The alignment of both pulsed- and continuous-wave Doppler was optimized to be parallel with flow. Pressure gradients were calculated using the simplified Bernoulli equation. AVA was calculated using the continuity equation. Stroke volume was calculated by multiplying the LV outflow tract area with the LV outflow tract time-velocity integral. The LV outflow tract diameter was measured in zoomed parasternal long-axis views in early systole at the level of aortic cusp insertion. The LV outflow tract time-velocity integral was recorded from the apical 5-chamber view, with the sample volume positioned  $\approx 5$  mm proximal to the aortic valve. LV dimensions were assessed from parasternal long-axis views by 2-dimensional-guided M mode using the leading-edge method at end diastole and end systole. LVEF was calculated using the Simpson biplane method. LV mass was estimated with an equation based on linear measurements normalized to body surface area (BSA).<sup>13</sup> Left atrial volume was measured at end systole (using the Simpson biplane method) and normalized to BSA. Systolic pulmonary artery pressure was calculated from the maximum peak tricuspid regurgitation velocity using the simplified Bernoulli equation.

### Follow-Up and End Points

Median (interquartile range) follow-up was 47 (24–80) months. The inclusion period was from 2000 to 2014. Information on follow-up was obtained yearly on the same period for the entire cohort, by direct patient interview, clinical examination, and/or repeated follow-up letters, questionnaires, and telephone calls to physicians, patients, and (if necessary) next of kin. A total of 246 (97%) of the surviving patients were followed up until the end of the study (2016), with an inclusion date corresponding to the date of baseline echocardiography (3% of patients were lost to follow-up). No patient was censored. The primary end point was all-cause mortality. Secondary end points were cardiovascular mortality and aortic valve replacement (AVR). Clinical decisions on medical management or referral for surgery were made by the Heart Team with the approval of the patient's cardiologist based on the European Society of Cardiology's guidelines<sup>6</sup> when AS had become severe.

### Statistical Analysis

Continuous variables are expressed as mean  $\pm$  SD or median (interquartile range), and categorical variables are expressed

as numbers and percentages. The relationship between baseline continuous variables and the various groups was explored using 1-way ANOVA tests. Mortality analyses were performed using Cox proportional hazards models. A predefined Cox proportional hazards model, including covariates with potential prognostic impact (age, sex, BSA, New York Heart Association class, prior AF, mean transaortic pressure gradient, LVEF, history of myocardial infarction, moderate-to-severe aortic valve calcification, Charlson comorbidity index, and AVR treated as a time-dependent variable), was used for multivariate mortality analyses (all data were complete for these variables). Event rates $\pm$ SEs were estimated using the Kaplan-Meier method and compared by 2-sided log-rank tests. Each patient with MAS was matched for the average survival (per year) of all patients of the same age and same sex from our region (Somme, department of 555 551 inhabitants, north of France). Control data were obtained from Somme life tables established on the basis of the 1999 population census, performed by the French Institute of National Statistics, and they represent the survival of the entire Somme general population.<sup>14,15</sup> Survival rates of patients with MAS were compared with the expected survival of people of the same age and sex in the Somme department. Relative survival was computed as the ratio of observed/expected survival (observed number of deaths in the population with MAS/expected number of deaths in the general population). The limit of statistical significance was  $P<0.05$ , and all tests were 2 tailed. Data were analyzed using SPSS 25.0 (SPSS Inc, Chicago, IL).

## Results

### Baseline Characteristics

The study population consisted of 508 patients: 287 men (56.5%) and 221 women (43.5%), with a mean $\pm$ SD age of 75 $\pm$ 11 years. Patients were mostly asymptomatic or minimally symptomatic (86.4% in New York Heart Association class 1–2). A total of 398 patients (78.3%) had a history of hypertension, 184 (36.2%) were diabetic, 236 (46.5%) had coronary artery disease, 171 (33.7%) had prior AF, and 39 (7.7%) had a history of myocardial infarction (Table 1). Mean $\pm$ SD AVA was 1.2 $\pm$ 0.15 cm<sup>2</sup>, mean $\pm$ SD transaortic pressure gradient was 24.8 $\pm$ 9 mm Hg, and mean $\pm$ SD peak aortic jet velocity was 3.2 $\pm$ 0.55 cm/s; and 276 patients (53%) had moderate-to-severe aortic valve calcification. Mean $\pm$ SD LVEF was 64 $\pm$ 8%, and mean $\pm$ SD left atrial volume index was 37 $\pm$ 20 mL/m<sup>2</sup>.

Patients who died during follow-up were older ( $P<0.001$ ), had a smaller BSA ( $P=0.001$ ), and had more comorbidities ( $P<0.001$ ) at baseline compared with surviving patients. Deceased patients more often had a history of AF ( $P<0.001$ )

and more often had moderate-to-severe aortic valve calcification ( $P=0.016$ ). No differences were observed between surviving and deceased patients in terms of AS severity (all  $P>0.20$ ), LV dimensions, and LVEF (all  $P>0.25$ ). Left atrial volume index ( $P=0.004$ ) was higher in deceased patients (Table 1). Data on AS progression were available in 317 patients (62.5%) during a mean $\pm$ SD follow-up of 42 $\pm$ 26 months. Mean $\pm$ SD annual increases of mean transaortic pressure gradient and peak aortic jet velocity were 6 $\pm$ 5 mm Hg (median, 4 mm Hg) and 0.33 $\pm$ 0.26 m/s (median, 0.24 m/s), respectively; and mean $\pm$ SD annual decrease of AVA was 0.13 $\pm$ 0.12 cm<sup>2</sup> (median, 0.09 cm<sup>2</sup>). Among these 317 patients, 139 had mild calcification, 144 had moderate calcification, and 34 had severe calcification at baseline. At follow-up (mean $\pm$ SD, 42 $\pm$ 26 months), 220 patients developed severe AS (AVA  $<1$  cm<sup>2</sup>): 70 of the baseline mild calcification group (50.4%), 120 of the baseline moderate calcification group (83.3%), and 30 of the baseline severe calcification group (88.2%) ( $P<0.001$ ).

### Outcome of MAS

A total of 255 deaths (50.2%) were recorded during follow-up, 101 of which were cardiovascular related (40%). Overall mortality rates were relatively high: 22 $\pm$ 3% at 2 years, 36 $\pm$ 2% at 4 years, and 47 $\pm$ 3% at 6 years of follow-up (Figure 1). The 6-year survival of patients with MAS was lower than the expected survival (53 $\pm$ 2% versus 65%). The 2-, 4-, and 6-year relative survivals (observed number of deaths in the population with MAS/expected number of deaths in the general population) were 88.6%, 84.2%, and 81.5%, respectively. On multivariate analysis, age (hazard ratio [HR], 1.05 [95% CI, 1.04–1.07];  $P<0.001$ ), prior AF (HR, 1.36 [95% CI, 1.05–1.76];  $P=0.019$ ), and Charlson comorbidity index (HR, 1.13 [95% CI, 1.07–1.22];  $P<0.001$ ) were associated with increased all-cause mortality (Table 2, model 1), whereas sex, BSA, New York Heart Association class, LVEF, baseline mean transaortic pressure gradient, moderate-to-severe valve calcification, and prior myocardial infarction were not (all  $P>0.30$ ). When AVR (performed in accordance with current guidelines), treated as a time-dependent variable, was added to the fully adjusted model, it was associated with better survival (HR, 0.38 [95% CI, 0.27–0.54];  $P<0.001$ ) (Table 2, model 2). Independent predictors of cardiovascular mortality were history of AF (HR, 1.90 [95% CI, 1.21–1.97];  $P=0.005$ ) and Charlson comorbidity index (HR, 1.18 [95% CI, 1.03–1.22];  $P<0.001$ ). The effect of LVEF was borderline ( $P=0.07$ ). Sex, BSA, New York Heart Association class, baseline mean transaortic pressure gradient, moderate-to-severe valve calcification, and prior myocardial infarction (all  $P>0.20$ ) were not independently predictive of cardiovascular mortality. When AVR (performed in accordance with current guidelines), treated as a time-dependent variable, was added to the fully adjusted model, it was associated with

**Table 1.** Baseline Demographic, Clinical, and Echocardiographic Characteristics of the Study Patients With MAS, According to Their Vital Status

Variable	Overall Population (n=508)	Living Patients (n=253)	Deceased Patients (n=255)	P Value by Cox Analysis
<b>Demographic data and symptoms</b>				
Age, y	75±11	72±11.5	79±9	<0.001
Male sex, % (n)	56.5 (287)	58 (147)	55 (140)	0.097
Body surface area, m <sup>2</sup>	1.91±0.22	1.94±0.2	1.88±0.23	0.001
NYHA, % (n)				
1–2	86.4 (439)	88.5 (224)	84.3 (215)	
3–4	13.6 (69)	11.5 (29)	15.7 (40)	0.338
<b>Medical history and risk factors</b>				
Hypertension, % (n)	78.3 (398)	78.3 (198)	78.4 (200)	0.306
Diabetes mellitus, % (n)	36.2 (184)	32.8 (83)	39.6 (101)	0.258
Hyperlipidemia, % (n)	48.4 (246)	56.1 (142)	40.8 (104)	<0.001
Smoking, % (n)	16.3 (83)	16.6 (42)	16.1 (41)	0.534
Coronary artery disease, % (n)	46.5 (236)	42.5 (107)	50.6 (129)	0.360
Myocardial infarction, % (n)	7.7 (39)	7.5 (19)	7.8 (20)	0.365
Left bundle branch block, % (n)	5.5 (28)	5.9 (15)	5.1 (13)	0.926
Prior atrial fibrillation, % (n)	33.7 (171)	24.1 (61)	43.1 (110)	<0.001
Heart failure, % (n)	8.9 (45)	9.1 (23)	8.6 (22)	0.123
Charlson comorbidity index	2.04±2.03	1.49±1.78	2.60±2.21	<0.001
<b>Echocardiographic parameters</b>				
<b>Aortic valve</b>				
Aortic valve area, cm <sup>2</sup>	1.2±0.15	1.21±0.15	1.2±0.15	0.277
Peak aortic jet velocity, m/s	3.2±0.55	3.2±0.59	3.1±0.51	0.212
Mean pressure gradient, mm Hg	24.8±9	25.5±10	24±8.5	0.128
Indexed stroke volume, mL/m <sup>2</sup>	44±10	44±11	44±9	0.968
Moderate-to-severe valve calcification, % (n)	53 (276)	41.8 (106)	66.7 (170)	0.016
<b>LV function</b>				
LV end-diastolic diameter, mm	48.6±7	48±7	49±7	0.253
LV end-systolic diameter, mm	30±6	29.7±6	30±7	0.968
Ejection fraction, %	64±8	63±7	64±8	0.387
Indexed LV mass, g/m <sup>2</sup> *	149±64	157±72	144±55	0.161
Left atrial volume index, mL/m <sup>2</sup> †	37±20	35±20	39±21	0.067
<b>Surgery</b>				
Aortic valve replacement, % (n)	22.3 (113)	35.3 (89)	9.4 (24)	<0.001

Continuous variables are expressed as mean±1 SD, and categorical variables are expressed as percentages (numbers). LV indicates left ventricular; MAS, moderate aortic stenosis; NYHA, New York Heart Association.

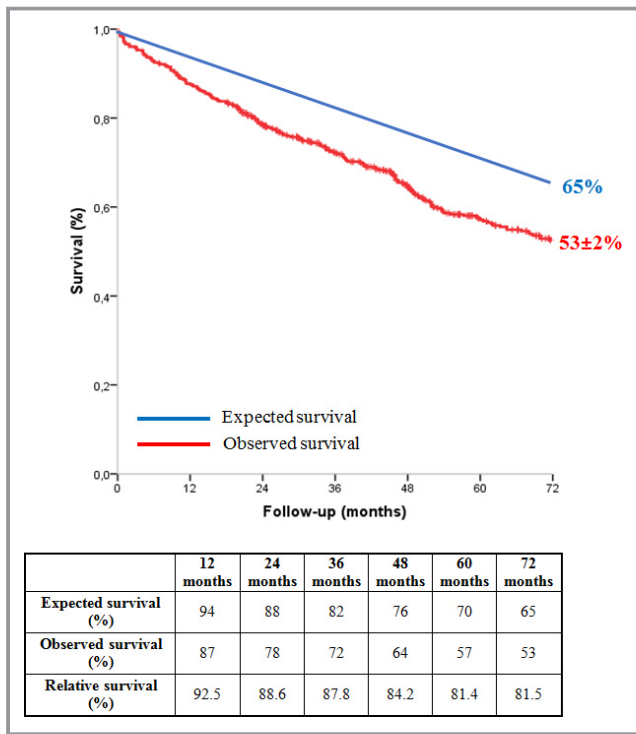
\*Missing data for 33 patients.

†Missing data for 56 patients.

lower cardiovascular mortality (HR, 0.49 [95% CI, 0.26–0.92];  $P=0.012$ ). When low flow (index stroke volume <35 mL/m<sup>2</sup>; found in 79 patients) was added to the fully adjusted model, it was not independently associated with all-cause ( $P=0.98$ ) or cardiovascular ( $P=0.54$ ) mortality.

The bicuspid or tricuspid character of AS, identified using echocardiography, was only available in 300 patients (34 had bicuspid aortic valves and 266 had tricuspid aortic valves). Patients with bicuspid aortic valves were younger ( $P<0.001$ ) and had a lower Charlson comorbidity index ( $P=0.038$ ). By





**Figure 1.** Survival of patients with moderate aortic stenosis compared with that of the age- and sex-matched general population. Relative survival was computed as the ratio of the observed/expected survival (observed number of deaths in the population with moderate aortic stenosis/expected number of deaths in the general population).

Kaplan-Meier analysis, patients with bicuspid valves had better survival than those with tricuspid valves (log-rank  $P=0.001$ ). However, after adjustment for age and comorbidity index, mortality was similar ( $P=0.50$ ).

### Aortic Valve Surgery

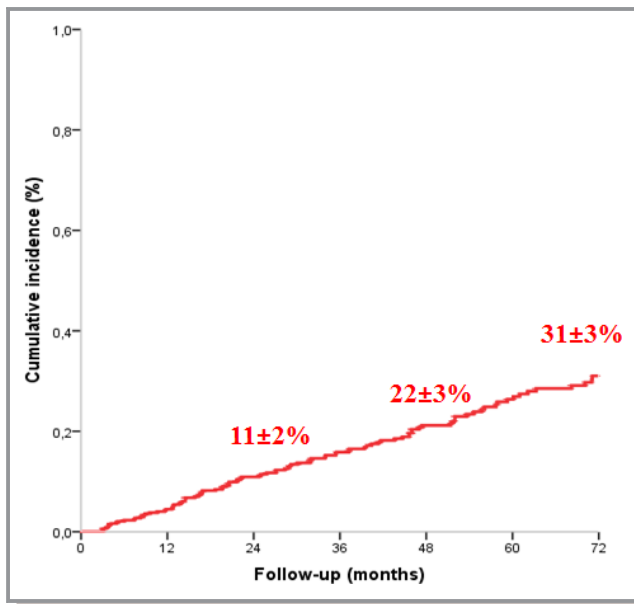
A total of 113 patients (22.2%) underwent AVR during follow-up: 98 for symptomatic severe AS (77 for dyspnea, 14 for angina, and 7 for syncope), 6 for severe AS with an exercise test showing symptoms related to AS, 4 for asymptomatic very severe AS, 3 for MAS and need for coronary artery bypass grafting, and 2 for MAS associated with aortic aneurysm >55 mm. Thirty-day perioperative mortality was 3.5% ( $n=4$ ). The mean±SD interval between inclusion and surgery was 37±22 months. On Kaplan-Meier analysis, the cumulative incidence of surgery was 11±2% at 24 months, 22±3% at 48 months, and 31±3% at 72 months (Figure 2). Operated patients were younger, had more severe AS (all  $P<0.001$ ), and more often presented moderate-to-severe calcification ( $P=0.036$ ) and greater LV end-diastolic ( $P=0.03$ ) and end-systolic ( $P=0.039$ ) diameters at baseline compared

**Table 2.** Relative Risk of All-Cause Death in Patients With MAS

Variables	Surgery	
	Multivariable Analysis	
	HR (95% CI)	P Value
<b>Model 1</b>		
Age (per 1-y increment)	1.05 (1.04–1.07)	<0.001
Male sex (yes vs no)	0.92 (0.70–1.22)	0.563
BSA (per 1-cm <sup>2</sup> decrement)	0.70 (0.35–1.44)	0.337
NYHA class (III–IV vs I–II)	1.10 (0.78–1.55)	0.600
Prior atrial fibrillation (yes vs no)	1.36 (1.05–1.76)	0.019
Mean pressure gradient (per 1-mm Hg increment)	1.01 (0.99–1.02)	0.760
Left ventricular ejection fraction (per 1% decrement)	0.99 (0.98–1.01)	0.584
Prior myocardial infarction (yes vs no)	1.04 (0.62–1.76)	0.880
Moderate-to-severe valve calcification (yes vs no)	1.19 (0.90–1.57)	0.222
Charlson comorbidity index (per 1-unit increment)	1.13 (1.07–1.22)	<0.001
<b>Model 2</b>		
Age (per 1-y increment)	1.04 (1.02–1.05)	<0.001
Male sex (yes vs no)	0.92 (0.70–1.21)	0.569
BSA (per 1-cm <sup>2</sup> decrement)	0.82 (0.41–1.61)	0.558
NYHA class (III–IV vs I–II)	1.04 (0.89–1.21)	0.614
Prior atrial fibrillation (yes vs no)	1.35 (1.05–1.73)	0.019
Mean pressure gradient (per 1-mm Hg increment)	1.01 (0.99–1.02)	0.543
Left ventricular ejection fraction (per 1% decrement)	0.99 (0.98–1.01)	0.783
Prior myocardial infarction (yes vs no)	1.01 (0.61–1.67)	0.980
Charlson comorbidity index (per 1-unit increment)	1.11 (1.05–1.18)	0.002
Moderate-to-severe valve calcification (yes vs no)	1.15 (0.86–1.51)	0.316
Aortic valve replacement (yes vs no)*	0.38 (0.27–0.54)	<0.001

Results of independent predictors of mortality. BSA indicates body surface area; HR, hazard ratio; MAS, moderate aortic stenosis; NYHA, New York Heart Association. \*Treated as a time-dependent variable.

with nonoperated patients (Table 3). Operated patients had fewer comorbidities ( $P=0.011$ ) and less often had a history of AF ( $P=0.014$ ) compared with nonoperated patients (Table 3).



**Figure 2.** Cumulative incidence of surgery during follow-up in the population of patients with moderate aortic stenosis.

## Discussion

The results of the present study show that patients with MAS present numerous cardiovascular risk factors (78.3% had hypertension, 36.2% were diabetics, and 48.3% had dyslipidemia). MAS is associated with a high rate of surgery (31±3%) at 72 months and with increased mortality compared with the general population, mainly related to comorbidities. Indeed, 255 patients (50.2%) died during follow-up, resulting in a lower survival than the expected survival (6-year survival of 53±2% versus 65%). On multivariate analysis, age, prior AF, and Charlson comorbidity index were associated with increased all-cause mortality, whereas AVR performed at the stage of severe AS in patients with an indication for surgery was associated with better survival.

Some studies focusing on mild-to-moderate AS have reported conflicting results, probably because of the different inclusion criteria used. In the study by Horstkotte and Loogen,<sup>16</sup> the mean interval between diagnosis and AVR was 13.4 years in a population of 142 patients with mild AS. Turina et al reported 100% and 80% 1- and 4-year survivals, respectively, after the diagnosis in a population of patients with mild-to-moderate AS.<sup>17</sup> These 2 studies suggest that mild-to-moderate AS is relatively benign, but they did not distinguish the 2 subgroups of mild AS and MAS. Kennedy et al,<sup>18</sup> in a small population of 66 patients considered to have MAS (with an AVA between 0.7 and 1.2 cm<sup>2</sup>, measured by cardiac catheterization), reported that 14 patients (21%) died of cardiovascular causes during the 35 months after diagnosis. However, some of these patients

had severe AS, according to the current definition.<sup>6,7</sup> In the study by Rosenhek et al,<sup>19</sup> which included 176 patients with mild-to-moderate AS (peak jet velocity between 2.5 and 3.9 m/s), 46% developed severe AS after 48±19 months of follow-up. These authors reported a 1.8-fold higher mortality than expected, and multivariate analysis showed that moderate-to-severe aortic valve calcification, coronary artery disease, and peak jet velocity were independent predictors of outcome.<sup>19</sup>

Otto et al<sup>20</sup> studied the natural history of 123 patients with asymptomatic AS stratified in 3 groups, according to baseline peak aortic jet velocity (<3, 3–4, and >4 m/s). They showed that the likelihood of remaining alive without valve replacement at 2 years was only 21±18% for a baseline jet velocity >4.0 m/s, compared with 66±13% for jet velocity between 3.0 and 4.0 m/s and 84±16% for jet velocity <3.0 m/s.<sup>20</sup> Moreover, the event-free survival of patients with peak jet velocity between 3 and 4 m/s, corresponding to patients with MAS, decreased drastically after 2 to 3 years. This study has undeniably emphasized that patients with MAS are at high risk of AVR.<sup>20</sup> Similar to Otto et al,<sup>20</sup> we observed that mortality and surgery rates increased progressively in patients with MAS and remained relatively low at 2 years (22% mortality and 11% surgery). Nevertheless, we did not observe a clear break in the curves after 2 to 3 years of follow-up. This difference can be explained by the fact that the results of Otto et al were largely driven by AVR (48 AVR and 8 deaths recorded after a mean follow-up of 2.5 years<sup>20</sup>). Mehrotra et al<sup>21</sup> investigated, using a composite end point (AVR or death), the prognosis of patients with AS and an ejection fraction ≥55%, separated into 3 groups according to AVA (<0.8, 0.8–0.99, and 1.0–1.3 cm<sup>2</sup>). The composite end point was observed in 21% of patients with MAS (AVA 1–1.3 cm<sup>2</sup>, n=81) at 3 years.<sup>21</sup> Our results, based on a larger number of patients, are in agreement with this study reporting a slightly higher rate of death or AVR at 3 years (28±2%). Compared with the study of Mehrotra et al,<sup>21</sup> our population was younger (75 versus 79 years) and the MAS definition was different (1–1.5 versus 1–1.3 cm<sup>2</sup>). Patients with MAS, in the study by Mehrotra et al,<sup>21</sup> had many cardiovascular risk factors: 91% had hypertension, 83% had dyslipidemia, and 25% had diabetes mellitus.

In a veteran cohort of 104 patients with MAS (AVA between 1 and 1.5 cm<sup>2</sup>) with a high level of comorbidity (49% with diabetes mellitus, 61% with coronary artery disease), Yeboor et al<sup>22</sup> reported that 30% of patients underwent AVR and 61% died, with a mean follow-up of 22 months. They concluded that MAS in this selected veteran population is associated with rapid progression and considerable mortality. This is the only study that has specifically focused on MAS, as defined by current guidelines.<sup>6,7</sup> Patients with LV dysfunction were not excluded, and the results of this study cannot be

**Table 3.** Baseline Demographic, Clinical, and Echocardiographic Characteristics of the Study Patients With MAS, According to Their Cardiac Management

Variable	Operated Patients (N=113)	Nonoperated Patients (N=395)	P Value
<b>Demographic data and symptoms</b>			
Age, y	69±11	77±10	<0.001
Male sex, % (n)	65.5 (74)	53.9 (213)	0.030
Body surface area, m <sup>2</sup>	1.98±0.2	1.89±0.22	<0.001
NYHA, % (n)			
1–2	82.3 (93)	87.6 (346)	
3–4	17.7 (20)	12.4 (49)	0.172
<b>Medical history and risk factors</b>			
Hypertension, % (n)	78.8 (89)	78.2 (309)	0.903
Diabetes mellitus, % (n)	35.4 (40)	36.5 (144)	0.837
Hyperlipidemia, % (n)	61.1 (69)	44.8 (177)	0.003
Smoking, % (n)	17.7 (20)	15.9 (63)	0.657
Coronary artery disease, % (n)	57.5 (65)	43.3 (171)	0.005
Myocardial infarction, % (n)	5.3 (6)	8.4 (33)	0.288
Left bundle branch block, % (n)	8 (9)	4.8 (19)	0.200
Prior atrial fibrillation, % (n)	23.9 (27)	36.5 (144)	0.014
Heart failure, % (n)	5.3 (6)	9.9 (39)	0.139
Charlson comorbidity index	1.61±1.56	2.16±2.13	0.011
<b>Echocardiographic parameters</b>			
Aortic valve			
Aortic valve area, cm <sup>2</sup>	1.18±0.15	1.22±0.15	<0.001
Peak aortic jet velocity, m/s	3.41±0.6	3.1±0.5	<0.001
Mean pressure gradient, mm Hg	29.3±11	23±8	<0.001
Indexed stroke volume, mL/m <sup>2</sup>	47±11	43±10	0.003
Moderate-to-severe valve calcification, % (n)	59.3 (67)	52.9 (209)	0.036
LV function			
LV end-diastolic diameter, mm	50±7	48±7.2	0.003
LV end-systolic diameter, mm	31±7	30±6	0.039
Ejection fraction, %	64±8	63±7	0.229
Indexed LV mass, g/m <sup>2</sup> *	158±73	147±62	0.142
Left atrial volume index, mL/m <sup>2</sup> †	38±18	37±21	0.478

Continuous variables are expressed as mean±1 SD, and categorical variables are expressed as percentages (numbers). LV indicates left ventricular; MAS, moderate aortic stenosis; NYHA, New York Heart Association.

\*Missing data for 33 patients.

†Missing data for 56 patients.

generalized, as 99% of patients in this cohort were men with multiple comorbidities.

AVR currently remains the only treatment for symptomatic severe AS, because, according to available data, the mean survival after onset of symptoms is only 2 to 3 years.<sup>5,23</sup> According to current European guidelines,<sup>6</sup> in the presence of significant calcification, mild and MAS should be reevaluated

yearly but intervals may be extended to 2 to 3 years in younger patients with mild AS and no significant calcification. US guidelines recommend serial echocardiography every 1 to 2 years for MAS and 3 to 5 years for mild AS.<sup>7</sup> The prognosis of patients with MAS may, therefore, not be as good as previously reported.<sup>18–20</sup> The results of the present study suggest that patients with MAS should be managed for their

cardiovascular risk factors and require close follow-up, especially when the AVA is close to 1 cm<sup>2</sup>.

## Limitations

Because follow-up data were obtained retrospectively, this study, therefore, presents the limitations inherent to this type of analysis. This study exclusively concerned patients with MAS and preserved LVEF without significant valve regurgitation, and results cannot be extrapolated to patients with concomitant LV dysfunction or significant regurgitation. Coexistence of MAS and LV dysfunction is not uncommon and may contribute to worsening myocardial function and symptoms because of increased afterload. Indeed, patients with MAS and LV dysfunction have poor outcome and high risk for clinical events.<sup>24</sup> There is an ongoing randomized trial (TAVR UNLOAD [Transcatheter Aortic Valve Replacement to Unload the Left Ventricle in Patients With Advanced Heart Failure]; NCT02661451) evaluating transcatheter AVR in patients with MAS, heart failure, and LVEF <50%.<sup>23</sup>

## Conclusion

This study provides important information about MAS, a condition that has not been exclusively studied in the past, as most previous studies mixed mild AS and MAS or used MAS as a comparison group for severe AS. The results show that patients with MAS have an increased mortality compared with the general population. This excess mortality is mainly related to associated comorbidities. Cardiovascular risk factors are frequent in these patients with MAS and must be appropriately managed. The cumulative incidence of AVR at 6 years is high, reaching 30%. Patients with an AVA close to 1 cm<sup>2</sup> should be followed up closely as AVR is associated with improved survival when these patients transition to severe AS and develop indications for surgery during follow-up.

## Disclosures

None.

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