ORIGINAL RESEARCH

Outcome of Normal-Flow Low-Gradient Severe Aortic Stenosis With Preserved Left Ventricular Ejection Fraction: A Propensity-Matched Study

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***Background*—**Normal-flow, low-gradient severe aortic stenosis (NF-LG-SAS), defined by aortic valve area <1 cm^2, mean gradient <40 mm Hg, and indexed stroke volume >35 mL/m^2, is the most prevalent form of low-gradient aortic stenosis (AS). However, the true severity of AS and the management of NF-LG-SAS are controversial. The aim of this study was to evaluate the outcome of patients with NF-LG-SAS compared with moderate AS (MAS) and with high-gradient severe-AS (HG-SAS).

***Methods and Results*—**A total of 154 patients with NF-LG-SAS, 366 with MAS (aortic valve area between 1.0 and 1.3 cm^2), and 1055 with HG-SAS were included. On multivariate analysis, after adjustment for covariates of prognostic importance, NF-LG-SAS patients did not exhibit an excess risk of mortality compared with MAS patients under medical management (hazard ratio=1.13 [95% CI, 0.82-1.56]; *P*=0.45) and under medical and surgical management (hazard ratio 1.06 [95% CI, 0.79-1.43]; *P*=0.70), even after further adjustment for aortic valve replacement (hazard ratio=1.09 [95% CI, 0.81-1.48]; *P*=0.56). The 6-year cumulative incidence of aortic valve replacement (performed in accordance with guidelines) was comparable between the 2 groups (39±4% for NF-LG-SAS and 35±3% for MAS, *P*=0.10). After propensity score matching (n=226), NF-LG-SAS and MAS patients also had comparable outcomes under medical (*P*=0.41) and under medical and surgical management (*P*=0.52). NF-LG-SAS had better outcomes than HG-SAS patients (adjusted hazard ratio 1.84 [95% CI, 1.18-2.88]; *P*<0.001).

***Conclusions*—**This study shows that patients with NF-LG-SAS have a comparable outcome to those with MAS when aortic valve replacement is performed during follow-up according to guidelines, mostly at the stage of HG-SAS. Rigorous echocardiographic assessment to rule out measurement errors and close follow-up are essential to detect progression to true severe AS in NF-LG-SAS. **(*J Am Heart Assoc*. 2019;8:e012301. DOI: 10.1161/JAHA.119.012301.)**

Key Words: moderate aortic stenosis • mortality • normal-flow, low-gradient aortic stenosis • outcome • surgery

Aortic stenosis (AS) is the most common valvular heart disease in developed countries and represents a contemporary health issue. Transthoracic echocardiography is the cornerstone of AS evaluation, but some inconsistencies exist concerning AS grading.[1,2] Current guidelines[3] define 4 categories of AS with preserved left ventricular ejection fraction (LVEF) according to mean aortic pressure gradient (MPG) and stroke volume index (SVi). The normal-flow, low-gradient severe AS (NF-LG-SAS) category is defined as aortic valve area (AVA) <1 cm^2, MPG <40 mm Hg, SVi >35 mL/m^2, and LVEF ≥50%. NF-LG-SAS is a common form of AS, accounting for 20% to 30% of all cases of severe AS with preserved LVEF in recent studies,[2,4] and it is the most prevalent form of low-gradient AS.[5] However, the management of NF-LG-SAS is strongly debated[6-13] due to the uncertainty concerning the true severity of AS, as recent studies suggest that these patients present true severe AS and may therefore benefit from aortic valve replacement (AVR) in the presence of symptoms.[7-10] Other authors consider that this entity is a moderate form of AS and that patients should consequently not be referred for AVR[6,11-14] to avoid unnecessary and potentially dangerous surgery. According to current European guidelines,[3] AVR is currently not indicated in patients with NF-LG-SAS and preserved LVEF. However, a group of

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Clinical Perspective

What Is New?

- Patients with normal-flow, low-gradient severe aortic stenosis (NF-LG-SAS) have comparable outcome to patients with moderate aortic stenosis even after propensity matching.
- The 6-year cumulative incidence of surgery is comparable between NF-LG-SAS and moderate aortic stenosis patients, but aortic valve replacement is performed earlier in NF-LG-SAS patients.
- Patients with NF-LG-SAS have better outcomes than patients with high-gradient severe AS under medical management and under medical and surgical management.

What Are the Clinical Implications?

- Patients with NF-LG-SAS should be considered as patients with moderate AS and managed as such.
- The key step is to rule out measurement errors during the initial echocardiography using a rigorous methodology and, when there is a doubt about the severity of aortic stenosis, to perform additional examinations.
- In NF-LG-SAS, watchful observation with echocardiographic monitoring after the diagnosis is essential to detect progression to high-gradient severe AS, and timely performance of surgery during follow-up should be considered as a therapeutic option for these patients.

experts from leading American learned societies in cardiology recommends, in a consensus paper published in 2017,[15] performing AVR for patients with symptomatic NF-LG-SAS.

In this context, the present study was designed to (1) evaluate the outcome of patients with NF-LG-SAS and preserved LVEF and (2) compare the prognosis of NF-LG-SAS patients with that of moderate AS (MAS) patients who are considered suitable for conservative management and with that of HG-SAS patients.

Methods

Population

The data that support the findings of this study are available from the corresponding author on reasonable request. Between 2000 and 2015, patients over the age of 18 years with a diagnosis of at least mild AS (aortic valve calcification with restricted systolic leaflet motion and AVA <2 cm^2) diagnosed in the echocardiography laboratories of 2 French tertiary centers were prospectively identified and included in an electronic database. The following patients were excluded: (1) patients with more than mild aortic and/or mitral regurgitation; (2) patients with prosthetic valves, congenital heart disease, supravalvular or subvalvular AS, or dynamic left ventricular (LV) outflow tract obstruction; (3) patients with LVEF <50%; and (4) patients who refused to participate in the study. A total of 2148 patients with AS and preserved LVEF (≥50%) were included. The present analysis was based on 154 patients with NF-LG-SAS, defined by AVA <1 cm^2, low gradient defined by MPG <40 mm Hg and normal flow defined by SVi >35 mL/m^2, 366 patients with MAS, defined by AVA 1.0 to 1.3 cm^2, and 1055 patients with HG-SAS (MPG>40mmHg) not operated on during the first 3 months after the baseline echocardiography.

Symptoms were ascertained by each patient's cardiologist at the time of baseline echocardiography. The Charlson comorbidity index was calculated for each patient.[16] Coronary artery disease was defined by the presence of a documented history of acute coronary syndrome, coronary artery disease previously confirmed by coronary angiography, or history of coronary revascularization. The study was approved by an independent ethics committee and conducted in accordance with institutional policies, national legal requirements, and the revised Declaration of Helsinki.

Echocardiography

All patients underwent comprehensive Doppler-echocardiography assessment using commercially available ultrasound systems. All echocardiograms were performed by senior cardiologists with expertise in valvular heart disease. LV outflow tract (LVOT) diameter was measured in zoomed parasternal long-axis views in early systole at the level of aortic cusp insertion.[17] Aortic flow was systematically recorded using continuous-wave Doppler from several views (apical 5-chamber, right parasternal, suprasternal, and epigastric).[18] The view identifying the highest velocities was used to determine peak velocity. Three consecutive measurements in patients in sinus rhythm or 5 consecutive measurements in patients in atrial fibrillation (AF) in this view were systematically averaged. The LVOT velocity-time integral was recorded using pulsed-wave Doppler from the apical 5-chamber view, with the sample volume positioned about 5 mm proximal to the aortic valve.[17] The alignment of both pulsed and continuous-wave Doppler was optimized to be parallel with aortic flow. Pressure gradients were calculated using the simplified Bernoulli equation. Stroke volume was calculated by multiplying the LVOT area with the LVOT velocity-time integral[17] and was indexed to body surface area (BSA). LVEF was measured by the Simpson biplane method.[19] LV mass was estimated by the formula on the basis of linear measurements and indexed to BSA.[19] Systolic pulmonary artery pressure was recorded from the maximum peak tricuspid regurgitation velocity in any view using the simplified Bernoulli equation.

Follow-Up

Median follow-up [25th-75th percentile] was 41 [20-70] months. Patients were followed by clinical consultations and echocardiography in the outpatient clinics of the 2 centers

according to current guidelines. A few patients were followed in public hospitals or private practices by referring cardiologists working in collaboration with the tertiary centers. Follow-up was complete up until death or the end of the study for 1433 patients (91%). Information on follow-up was retrospectively obtained by direct patient interview or by repeated follow-up letters and questionnaires. Given the retrospective nature of the study, informed consent was waived, and all of the patients agreed to participate in the study when contacted for follow-up. The study end point was overall survival after diagnosis at baseline echocardiography. Survival analysis under medical management continued until last follow-up on medical management (censored at surgery). Survival under medical and surgical management continued until the last follow-up. Clinical decisions regarding medical management and referral for surgery were taken by the heart team with the approval of the patients' cardiologists in accord with current practice guidelines.[3]

Statistical Analyses

SPSS version 25 software (IBM, Armonk, NY) was used for statistical analysis. The study population was divided into 2 groups according to the type of AS: NF-LG-SAS or MAS. Continuous variables were expressed as mean±SD or median (interquartile range), and categorical variables were expressed as numbers (percentages). The relationship between continuous baseline variables and the various groups was explored using 1-way ANOVA or Kruskal-Wallis test. Pearson chi-squared statistic or Fisher exact test was used to examine the association between baseline categorical variables and the various groups. The start of follow-up for survival analysis was baseline echocardiography. Event rates±standard error in the 2 groups were estimated using the Kaplan-Meier method and were compared using 2-sided log-rank tests. Univariate and multivariate analyses of times to events were performed using Cox proportional hazards models. Covariates considered to have a potential prognostic impact on an epidemiological basis and all other covariates associated with mortality ($P<0.10$) were entered in the model for multivariable analysis. These covariates were age, sex, BSA, New York Heart Association class (III-IV versus I-II), diabetes mellitus, prior AF, Charlson comorbidity index, LVEF, LV end-diastolic diameter, LV mass index, and left atrial volume index. AVR, treated as a time-dependent covariate, was added in a second model.

The imbalance in baseline variables (with the exception of AS severity parameters) between NF-LG-SAS and MAS patients was reduced by use of propensity scores. We estimated propensity scores for each of the 520 patients using a multivariate logistic model, as previously described.[20] Propensity scores were used to match each NF-LG-SAS patient with a unique control with a propensity score within 2%. Each patient with NF-LG-SAS was first matched with another patient with MAS with a similar 5-digit propensity score, and matched patients were removed from the database. This procedure was repeated in the remaining patients with successive matching by 4-, 3-, and 2-digit scores. One hundred thirteen (73.4%) of the 154 patients with NF-LG-SAS were successfully matched. Baseline characteristics of the 2 resulting groups after matching were compared using Student t tests and chi-squared tests, as appropriate. Mean propensity scores between patients with NF-LG-SAS (0.66844 [0.59532-0.75897]) and patients with MAS (0.66859 [0.59563-0.75882]) were not statistically different ($P=0.97$).

Patients with NF-LG-SAS were also compared with the 1055 consecutive patients diagnosed with high gradient (MPG ≥40 mm Hg) severe AS (not operated on during the first 3 months after the baseline echocardiography) of our database. Univariate and multivariate analyses of times to events were performed using the same Cox proportional hazard models as those described above. The limit of statistical significance was $P<0.05$. All tests were 2-tailed.

Results

Baseline Characteristics of NF-LG-SAS and MAS Patients

Baseline demographic, clinical, and echocardiographic characteristics of the 154 patients with NF-LG-SAS and the 366 patients with MAS are presented in Table 1.

Compared with patients with MAS, patients with NF-LG-SAS were older ($P=0.001$), more often women ($P=0.03$), and had lower BSA ($P<0.001$). There was no significant difference between groups in term of New York Heart Association class ($P=0.47$), hypertension ($P=0.26$), diabetes mellitus ($P=0.17$), prior AF ($P=0.40$), coronary artery disease ($P=0.12$), and Charlson comorbidity index ($P=0.38$). BNP and serum creatinine were comparable between groups ($P=0.52$ and 0.93, respectively) (Table 1).

On echocardiography, median AVA was 0.90 and 1.12 cm^2 in the NF-LG-SAS and MAS groups, respectively ($P<0.001$). Transaortic MPG and peak velocity were higher in the NF-LG-SAS group (both $P<0.001$), and the dimensionless index was lower ($P<0.001$). No significant difference was observed between groups for SVi ($P=0.13$), LVEF ($P=0.90$), LV end-diastolic ($P=0.89$), and end-systolic ($P=0.70$) diameters. Indexed LV mass and indexed left atrial volume were both higher in the NF-LG-SAS group ($P=0.041$ and 0.050, respectively) (Table 1).

On multivariable logistic regression analysis, propensity scores were estimated for each of the 154 patients with NF-LG-SAS, and 113 patients were successfully matched. Baseline characteristics of the matched population are presented in Table 2. After this matching procedure, no

Table 1. Baseline Characteristics of the Study Population Before Matching According to the Aortic Stenosis Form: NF-LG-SAS and MAS

Variables	Before Matching		
	NF-LG-SAS (n=154)	MAS (n=366)	*P* Value
Demographics, baseline data, and symptoms			
Age, y	79±9	76±11	0.001
Male sex, n (%)	67 (43.5)	194 (53.0)	0.03
Body surface area, m^2	1.82±0.2	1.91±0.2	<0.001
NYHA, n (%)			
I-II	129 (83.8)	309 (84.4)	0.47
III-IV	25 (16.2)	57 (15.6)	
Medical history and risk factors			
Hypertension, n (%)	125 (81.2)	286 (78.1)	0.26
Diabetes mellitus, n (%)	47 (30.5)	129 (35.2)	0.17
Dyslipidemia, n (%)	71 (46.1)	175 (47.8)	0.40
Coronary artery disease, n (%)	79 (51.3)	165 (45.1)	0.12
Prior myocardial infarction, n (%)	14 (9.1)	29 (7.9)	0.39
Prior atrial fibrillation, n (%)	54 (35.1)	122 (33.3)	0.39
Charlson comorbidity index	2.06±2.0	2.1±2.0	0.36
Biological parameters			
BNP, pg/mL	209 (114-876)	228 (93-581)	0.52
Serum creatinine, μmol/L	88 (71-117)	87 (73-116)	0.93
Echocardiography and Doppler parameters			
Aortic valve			
Aortic valve area, cm^2	0.90 (0.82-0.97)	1.12 (1.06-1.20)	<0.001
Peak aortic jet velocity, m/s	3.6 (3.3-3.8)	3.2 (2.8-3.7)	<0.001
Transaortic mean pressure gradient, mm Hg	32 (26-36)	25 (19-32)	<0.001
Dimensionless index	0.25 (0.22-0.27)	0.29 (0.26-0.33)	<0.001
Indexed stroke volume, mL/m^2	41 (38-45)	43 (37-49)	0.13
Left-sided heart evaluation			
LV end-diastolic diameter, mm	48 (44-52)	49 (44-53)	0.89
LV end-systolic diameter, mm	30 (26-33)	30 (26-33)	0.70
Ejection fraction, %	65 (60-68)	64 (58-69)	0.90
Indexed LV mass, g/m^2	117 (99-147)	110 (93-136)	0.041
Indexed left atrial volume, mL/m^2	42 (33-54)	40 (30-49)	0.050

Continuous normally distributed variables are expressed as mean±1 SD; nonnormally distributed continuous variables are expressed as median (25th-75th percentiles), and categorical variables as percentages and counts. BNP indicates B-type natriuretic peptide; LV, left ventricular; MAS, moderate aortic stenosis; NF-LG-SAS, normal-flow, low-gradient severe aortic stenosis; NYHA, New York Heart Association class.

significant difference in terms of baseline variables was observed between the 2 groups.

Comparison of Outcome of NF-LG-SAS and MAS

Survival Under Medical Management

Median follow-up under medical management was 30 [13-56] months, and 238 deaths were recorded during follow-up. Six-year survival rates were 40±6% for the NF-LG-SAS group and 47±3% for the MAS group (*P*=0.071). On multivariate analysis, after adjustment for age, sex, BSA, symptoms, diabetes mellitus, prior AF, Charlson comorbidity index, LVEF, LV end-diastolic diameter, LV mass index, and left atrial volume index, patients with NF-LG-SAS did not exhibit an excess of mortality risk on medical management (adjusted hazard ratio [HR] 1.13 [95% CI, 0.82-1.56], *P*=0.449) compared with MAS patients (Figure 1, Table 3).

Table 2. Baseline Characteristics of the Propensity-Matched Cohort According to the Aortic Stenosis Form: NF-LG-SAS and MAS

Variables	After Matching		
	NF-LG-SAS (n=113)	MAS (n=113)	*P* Value
Demographics, baseline data, and symptoms			
Age, y	78±9	77±9	0.62
Male sex, n (%)	57 (50.4)	56 (49.6)	>0.99
Body surface area, m^2	1.87±0.22	1.86±0.21	0.93
NYHA, n (%)			
I-II	95 (84.1)	91 (80.5)	0.60
III-IV	18 (15.9)	22 (19.5)	
Medical history and risk factors			
Hypertension, n (%)	92 (81.4)	85 (75.2)	0.33
Diabetes mellitus, n (%)	34 (30.1)	30 (26.5)	0.66
Dyslipidemia, n (%)	53 (46.9)	55 (48.7)	0.89
Coronary artery disease, n (%)	61 (54.0)	65 (57.5)	0.69
Prior myocardial infarction, n (%)	8 (7.1)	7 (6.2)	>0.99
Prior atrial fibrillation, n (%)	41 (36.3)	37 (32.7)	0.68
Charlson comorbidity index	2.1±2.1	2.1±2.0	0.95
Echocardiography and Doppler parameters			
Indexed stroke volume, mL/m^2	41 (37-45)	42 (36-47)	0.57
LV end-diastolic diameter, mm	50 (45-53)	48 (43-53)	0.48
LV end-systolic diameter, mm	30 (27-33)	29 (26-33)	0.57
Ejection fraction (%)	65 (60-69)	65 (58-70)	0.88
Indexed LV mass, g/m^2	116 (98-144)	117 (95-147)	0.81
Indexed left atrial volume, mL/m^2	41 (33-52)	40 (31-53)	0.57

Continuous normally distributed variables are expressed as mean±1 SD, nonnormally distributed continuous variables are expressed as median (25th-75th percentiles), and categorical variables as percentages and counts. LV indicates left ventricular; MAS, moderate aortic stenosis; NF-LG-SAS, normal-flow, low-gradient severe aortic stenosis; NYHA, New York Heart Association class.

Survival Under Medical and Surgical Management

Median follow-up under medical and surgical management was 41 [20-70] months. During follow-up, AVR was performed in 126 patients (24.2%): 110 had surgical AVR (87%) and 16 transcatheter AVR (13%). The mean interval between inclusion and surgery was shorter for the NF-LG-SAS group (14 [6-23] months) than for the MAS group (24 [13-47] months) (*P*=0.016). On Kaplan-Meier analysis, the 72-month cumulative incidence of surgery was comparable (39±4% for NF-LG-SAS patients and 35±3% for MAS patients; log-rank *P*=0.10) (Figure 2). However, NF-LG-SAS patients get AVR earlier in the follow-up compared with MAS patients (25% versus 14% at 24 months; *P*<0.001, 31% versus 23% at 48 months; *P*=0.03). In the MAS group the indications for AVR performed during follow-up were (1) symptomatic high-gradient severe AS (n=68; 77.3%), (2) asymptomatic high-gradient severe AS with either rapid hemodynamic progression (n=5; 5.7%), LVEF <50% (n=2; 2.2%), or an exercise test showing symptoms related to AS (n=6; 6.8%), (3) asymptomatic very severe AS (peak velocity >5 m/s) (n=4; 4.5%), and (4) MAS and need for coronary artery bypass graft or ascending aorta surgery (n=3; 3.5%). In the NF-LG-SAS group the indications for AVR performed during follow-up were (1) high-gradient (MPG ≥40 mm Hg) severe AS with onset/worsening of symptoms (n=34; 89.5%), (2) asymptomatic high-gradient severe AS with an exercise test showing symptoms related to AS (n=2; 5.3%), and (3) NF-LG-SAS with worsening symptoms (n=2; 5.2%).

A total of 261 deaths were recorded during follow-up (74 in the NF-LG-SAS group [48.1%] and 187 in the MAS group [51.1%]). Six-year survival rates were 46±5% for the NF-LG-SAS group and 50±3% for the MAS group (*P*=0.185). On multivariate analysis, NF-LG-SAS was not identified as an independent predictor of mortality (adjusted HR 1.06 [95% CI, 0.79-1.43], *P*=0.70) compared with MAS. After further adjustment for AVR treated as a time-dependent covariate, NF-LG-SAS was still not predictive of mortality (adjusted HR 1.09 [95% CI, 0.81-1.48], *P*=0.565) (Table 3).

Propensity Outcome Analysis of NF-LG-SAS and MAS

Survival Under Medical Management

Median follow-up under medical management was 27 [12-51] months, and 110 deaths were recorded during follow-up. Six-year survival rates were 39±7% for the NF-LG-SAS group and 41±6% for the MAS group (log-rank *P*=0.415) (Figure 3).

Survival Under Medical and Surgical Management

Median follow-up under medical and surgical management was 36 [20-66] months, with 123 deaths recorded. Six-year survival rates were 46±6% for the NF-LG-SAS group and 42±5% for the MAS group (log-rank *P*=0.521) (Figure 4).

Comparison of Outcome of NF-LG-SAS and HG-SAS

The comparison of baseline characteristics between NF-LG-SAS patients and high-gradient severe AS (HG-SAS) patients is displayed in Table S1.

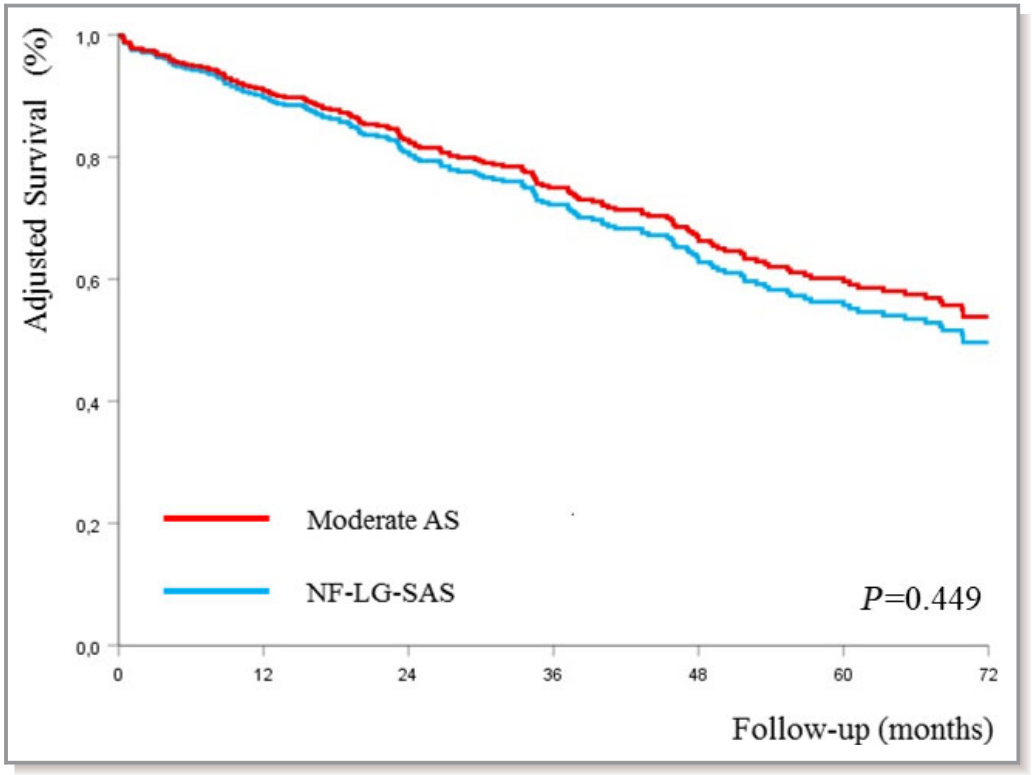

Figure 1. Adjusted survival curves in the study population under medical management according to the type of aortic stenosis (moderate AS or NF-LG-SAS). AS indicates aortic stenosis; NF-LG-SAS, normal-flow, low-gradient severe AS.

On multivariate analysis, after adjustment for age, sex, BSA, symptoms, diabetes mellitus, prior AF, Charlson comorbidity index, LVEF, LV end-diastolic diameter, LV mass index, and left atrial volume index, patients with HG-SAS displayed significant excess mortality under medical management (adjusted HR 1.84 [95% CI, 1.18-2.88], $P<0.001$) compared with NF-LG-SAS patients. After adjustment for the variables mentioned above and AVR treated as a time-dependent variable, patients with HG-SAS still exhibit an excess of mortality risk under medical and surgical management (adjusted HR 1.46 [95% CI, 1.06-2.04], $P<0.001$) compared with NF-LG-SAS patients (Figure 5).

Discussion

The results of this study show that patients with NF-LG-SAS (AVA <1 cm^2, MPG <40 mm Hg, SVi >35 mL/m^2) have a comparable survival to that of MAS patients (AVA 1-1.3 cm^2), and the results remained unchanged after propensity score matching. Our observation strategy for NF-LG-SAS patients resulted in a comparable outcome to that of MAS patients when AVR was performed during follow-up according to guidelines,[3] mostly at the stage of HG-SAS. The 6-year cumulative incidence of surgery was comparable between the 2 groups. However, AVR was performed earlier in NF-LG-SAS patients. Moreover, patients with NF-LG-SAS had better outcomes than patients with HG-SAS under medical management and under medical and surgical management.

In severe AS a low gradient is expected in the presence of a low-flow state, as the MPG is highly flow dependent. However, a low gradient in the presence of normal flow and severe AS is intriguing. Several explanations can be proposed, particularly measurement errors and inconsistencies in guideline criteria.[2,21,22] Indeed, the echocardiographic assessment of AS is difficult and may lead to underestimation or overestimation of AS parameters, thereby resulting in misclassification of AS severity with a risk of inappropriate management. The most common error is related to evaluation of LVOT diameter, which can sometimes be difficult to assess due to the presence of calcifications and/or poor echogenicity. A difference of a few millimeters results in a significant change in AVA because the diameter value is squared and estimation of AVA assumes that LVOT area has a circular shape. Various data derived from tridimensional echocardiography,[23] cardiac computed tomography,[24] and magnetic resonance imaging[25,26] have shown that the LVOT may have an elliptic shape, resulting in a risk of significant underestimation of LVOT area by using bidimensional echocardiography. Chin et al[25] showed that echocardiography significantly underestimated LVOT area and

Table 3. Independent Predictors of Overall Mortality on Cox Multivariate Analysis Under Medical and Surgical Management in Patients With Moderate AS and Patients With Normal-Flow Low-Gradient AS

Variables	All-Cause Mortality	
	Multivariate Analysis	
	Adjusted HR (95% CI)	*P* Value
Medical management		
Age (per 1-y increment)	1.06 (1.04-1.08)	<0.001
Male sex	0.77 (0.55-1.07)	0.122
Body surface area (per 0.1-m^2 increment)	0.69 (0.30-1.56)	0.372
NYHA class III-IV (vs I-II)	1.90 (1.37-2.65)	<0.001
Diabetes mellitus (yes vs no)	1.25 (0.91-1.70)	0.165
Prior atrial fibrillation (yes vs no)	1.09 (0.80-1.42)	0.587
Charlson comorbidity index (per 1-unit increment)	1.14 (1.06-1.23)	<0.001
LV end-diastolic diameter (per 1-mm decrement)	0.98 (0.96-1.01)	0.224
Ejection fraction (per 1% decrement)	0.98 (0.96-1.01)	0.107
LV mass index (per 10 g/m^2 increment)	1.03 (0.98-1.10)	0.090
Left atrial volume index (per 1 mL/m^2 increment)	1.01 (1.00-1.02)	0.060
Normal-flow, low-gradient severe AS	1.13 (0.82-1.56)	0.449
Medical and surgical management		
Age (per 1-year increment)	1.06 (1.04-1.08)	<0.001
Male sex	0.84 (0.62-1.13)	0.249
Body surface area (per 0.1 m^2 increment)	0.82 (0.39-1.73)	0.611
NYHA class III-IV (vs I-II)	1.95 (1.43-2.68)	<0.001
Diabetes mellitus (yes vs no)	1.08 (0.81-1.44)	0.606
Prior atrial fibrillation (yes vs no)	1.10 (0.83-1.47)	0.512
Charlson comorbidity index (per 1-unit increment)	1.10 (1.03-1.18)	0.007
LV end-diastolic diameter (per 1-mm decrement)	1.00 (0.90-1.03)	0.626
Ejection fraction (per 1% decrement)	0.99 (0.97-1.00)	0.177
LV mass index (per 10 g/m^2 increment)	1.05 (0.97-1.12)	0.110
Left atrial volume index (per 1 mL/m^2 increment)	1.01 (0.99-1.02)	0.078
Aortic valve replacement (yes vs no)	0.34 (0.24-0.49)	<0.001
Normal-flow low-gradient severe AS	1.09 (0.81-1.48)	0.565

AS indicates aortic stenosis; HR, hazard ratio; LV, left ventricular; NYHA, New York Heart Association.

therefore stroke volume and AVA, compared with magnetic resonance imaging. This underestimation of LVOT area could explain >40% of patients with discordant small-AVA low-gradient AS and preserved LVEF.[25] In the study by Maes et al[26] based on a magnetic resonance and echocardiography hybrid technique, 55% of patients with NF-LG-SAS were reclassified as MAS when a 1-cm^2 cut point defined severe AS when the LVOT area measured by cardiac magnetic resonance was entered into the continuity equation. Therefore, in the presence of an asymmetric LVOT, patients may be categorized by echocardiography as NF-LG-SAS when they actually have MAS. In our opinion, other imaging modality should be used when discussing AVR in NF-LG-SAS to eliminate an elliptical LVOT leading to a risk of underestimation of AVA. Interestingly, a recent study using computed tomography for LVOT area measurement and Doppler for flow measurements reported that the AVA cut-point value to define severe AS was higher, of 1.2 cm^2, when this hybrid method was used compared with the echocardiographic continuity equation method.[27] The second potential error concerns the positioning of the pulsed Doppler sample volume during measurement of the LVOT velocity-time integral, which led to possible underestimation or overestimation of the velocity-time integral and therefore AVA. Another classic situation is underestimation of the MPG when a multiview approach is not systematically performed, because of misalignment between the ultrasound beam and aortic flow.[17,28] In our study, we systemically performed careful measurements of LVOT diameter on zoomed parasternal long-axis views and used multiple acoustic windows for continuous-wave Doppler, including the right parasternal window using a Pedoff probe. This rigorous methodology can probably explain our relatively low proportion of NF-LG-SAS (15% of patients with AVA <1 cm^2) compared with recent studies, in which this form represents 20% to 30% of the AS population with AVA <1 cm^2.[2,4] In our opinion, most NF-LG-SAS patients are in fact MAS patients, and only a minority of these patients have severe AS. A rigorous approach is required to avoid missing this subset of patients with truly severe AS. The second step after ruling out measurement error in NF-LG-SAS is to eliminate a severe AS using other imaging modalities. In this setting, the calcium score assessed by multislice computed tomography is of great utility, as severe AS is unlikely for a calcium score <800 in women and <1600 in men.[3] Some authors consider that the flow rate (ie, stroke volume divided by LV ejection time) more accurately reflects the true AVA in suspected low-gradient severe AS.[29] The MPG is related to the SVi but also to heart rate (and consequently to ejection time), and some patients might have a normal SVi (>35 mL/m^2) but a reduced transvalvular flow rate, resulting in a low gradient. A possible explanation for the AVA-gradient discordance in some NF-LG-SAS patients might therefore be a reduced flow rate. Accordingly, some

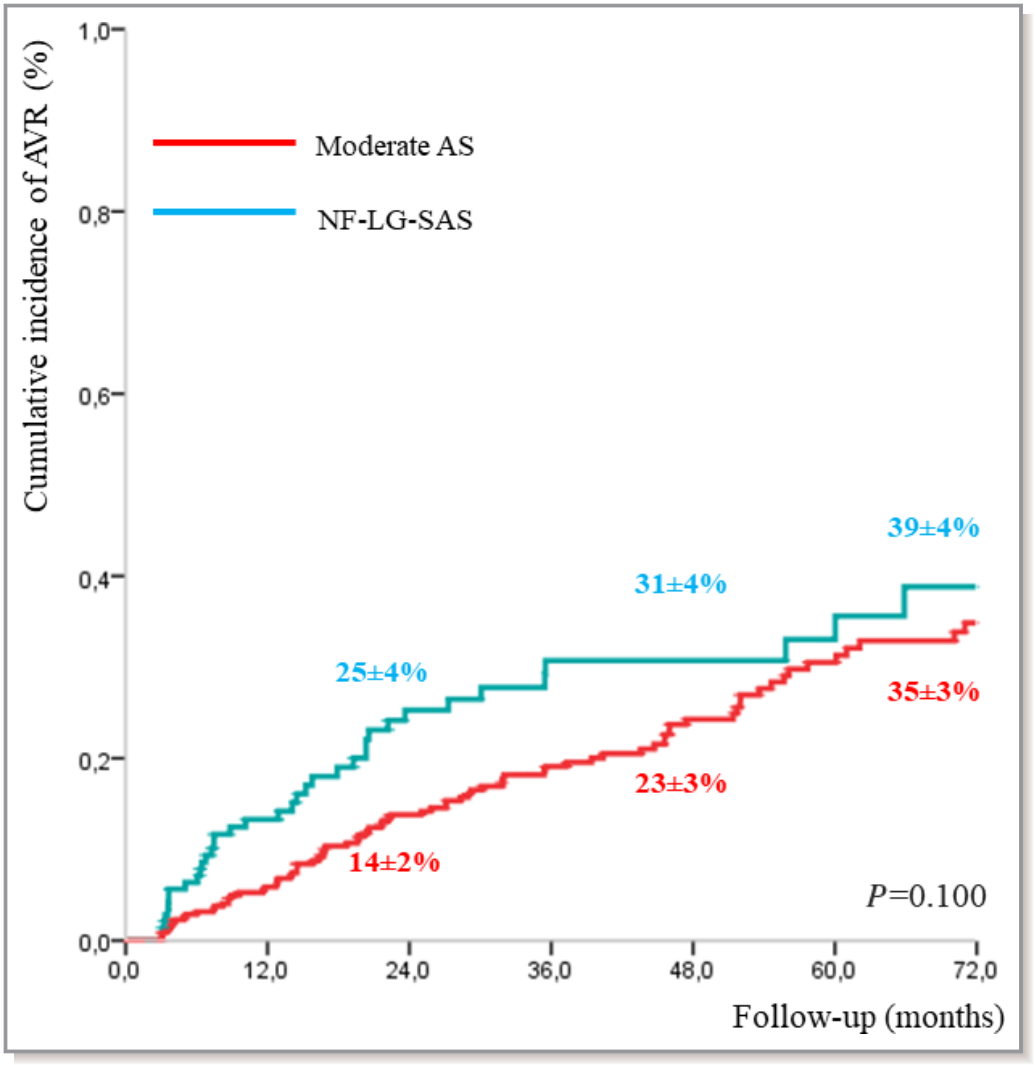

Figure 2. Cumulative incidence of aortic valve replacement during follow-up in the study population (n=520) according to the type of aortic stenosis (moderate AS or NF-LG-SAS). AS indicates aortic stenosis; AVR, aortic valve replacement; NF-LG-SAS, normal-flow, low-gradient severe AS.

authors[30,31] have suggested the use of low-dose dobutamine stress echocardiography or preload stress echocardiography in patients with NF-LG-SAS and low flow rate <200 mL/s to rule out severe AS. However, in a recent cohort of 529 patients with symptomatic severe AS with preserved LVEF, the proportion of NF-LG-AS with a low flow rate was about 20%, and flow rate was not superior to SVi in predicting outcomes.[32]

The prognosis and management of NF-LG-SAS are subjects of debate. Several studies using transthoracic echocardiography have suggested a poor outcome of this NF-LG-SAS form.[7-10] In medically managed patients with symptomatic low-gradient severe AS, a mortality rate of 53% with a mean follow-up of 27.5 months has been reported, with similar outcomes for NF-LG-SAS and low-flow low-gradient AS patients.[8] A recent meta-analysis[7] suggested that the prognosis of NF-LG-SAS is comparable to that of HG-SAS and reported a 52% reduction of the relative risk of mortality when AVR was performed in this population.[7] However, these results should be interpreted with caution, as these authors in this meta-analysis[7] compared several observational studies based on different populations. In addition, they did not analyze the outcome according to the type of intervention (surgical or transcatheter AVR) and, more importantly, in these studies AVR was mostly performed in accordance with guidelines and therefore not at the stage of NF-LG-SAS. Zusman et al[9] recently reported, in a population of symptomatic NF-LG-SAS patients, that AVR performed within 6 months after the diagnosis was associated with a reduction of all-cause and cardiovascular mortality compared with conservative management. However, on multivariate analysis, only transcatheter AVR was associated with better outcome, and surgical AVR was not.[9] These studies led a group of

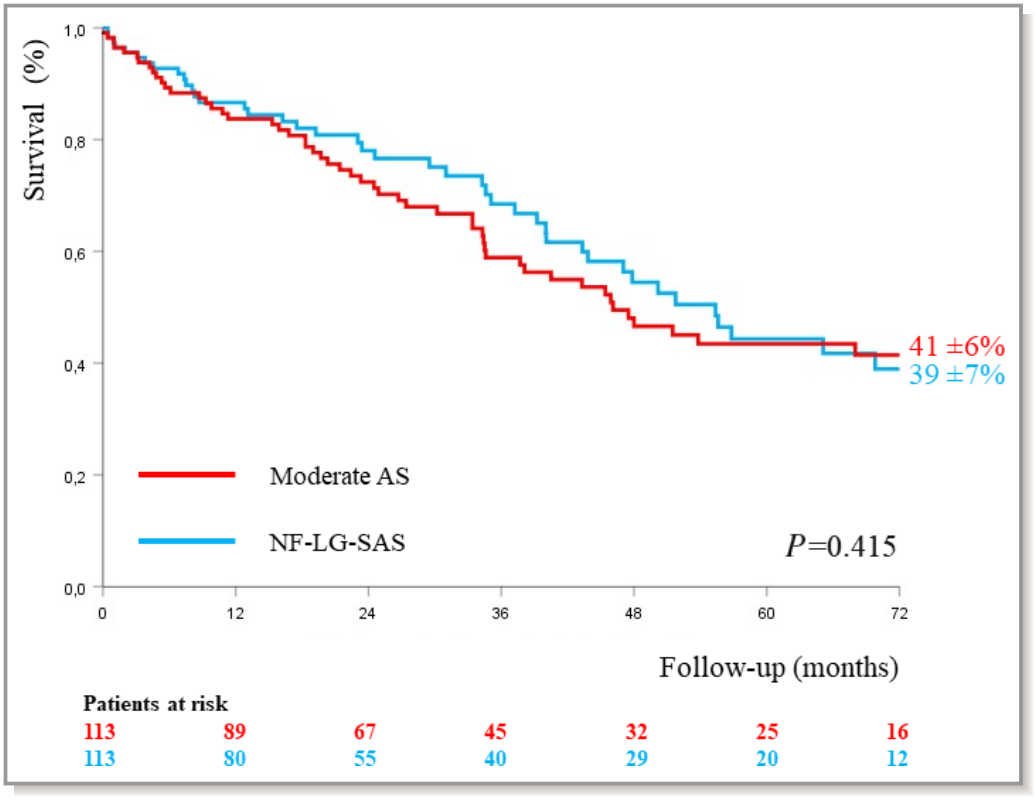

Figure 3. Kaplan-Meier survival curves according to the type of aortic stenosis (moderate AS or NF-LG-SAS) under medical management in the propensity-matched cohort (n=226). AS indicates aortic stenosis; NF-LG-SAS, normal-flow, low-gradient severe AS.

experts from leading American learned societies to consider surgery for symptomatic NF-LG-SAS patients after confirmation of the internal coherence of the AVA, flow, and gradient measurements, with evidence of a severely calcified valve.[15]

Patients with NF-LG-SAS are mostly elderly women with a low BSA, less concentric LV hypertrophy, less severe left atrial dilatation, and less severely impaired systolic longitudinal function compared with other forms of severe AS.[4,12] Barone-Rochette et al,[33] using cardiac magnetic resonance imaging, reported that these patients had larger AVA, less hypertrophy, and less concentric remodeling compared with high-gradient AS, suggesting a less severe form of AS. Accordingly, current European guidelines consider that patients with NF-LG-SAS generally only have MAS and should not be referred for AVR.[3] As previously reported,[4,34] the present study confirmed that patients with HG-SAS experienced higher mortality than NF-LG-SAS patients under medical management and under medical and surgical management. An ancillary study of the SEAS trial[11] compared asymptomatic MAS patients with asymptomatic low-gradient severe AS patients and found no difference in terms of aortic valve–related events after 46 months of follow-up. Kang et al[13] recently studied 284 symptomatic patients with NF-LG-SAS and, after 5 years of follow-up, found that overall and cardiovascular mortality were not significantly different between a watchful observation strategy and an early AVR strategy. Accordingly, in a recent meta-analysis, Zheng et al[35] concluded that patients with NF-LG-SAS had similar prognosis to those with MAS. Moreover, in this pooled analysis, AVR was most effective in normal-flow high-gradient-SAS than in NF-LG-SAS.[35] The present study demonstrated that patients with NF-LG-SAS (AVA <1 cm^2, MPG <40 mm Hg, SVi >35 mL/m^2) have a comparable outcome to that of MAS patients (AVA 1-1.3 cm^2) with conservative and surgical management. Furthermore, the 6-year cumulative incidence of AVR was comparable to that of patients with MAS. However, AVR was performed earlier in NF-LG-SAS compared with MAS patients, suggesting that these patients need closer clinical and echocardiographic monitoring than MAS patients.

Limitations

This study is subject to the limitations inherent to the analysis of retrospective follow-up data. However, cardiologists with expertise in valvular heart disease performed diagnosis and follow-up, and surgical decisions were made by the heart team with the approval of the patient's physicians, in accordance with current European guidelines. Given the low

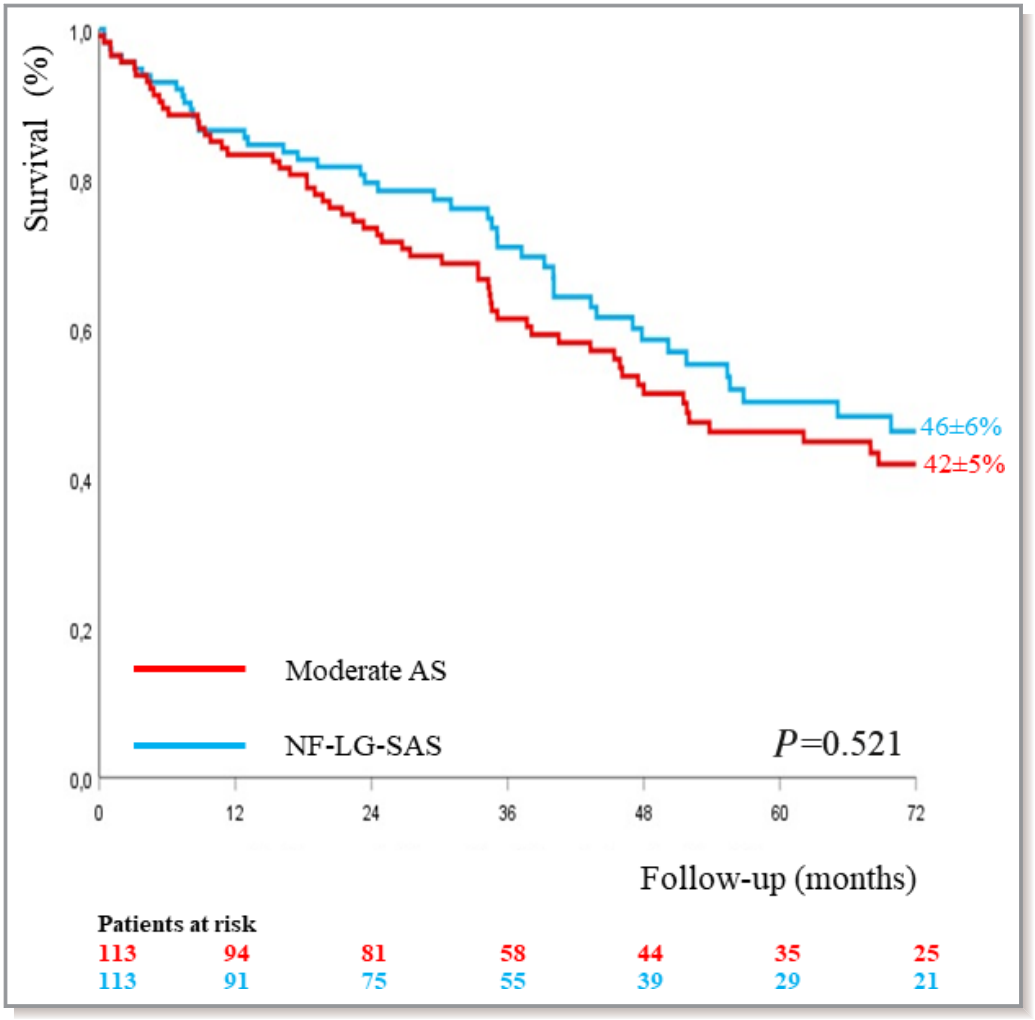

Figure 4. Kaplan-Meier survival curves according to the type of aortic stenosis (moderate AS or NF-LG-SAS) under medical and surgical management in the propensity-matched cohort (n=226). AS indicates aortic stenosis; NF-LG-SAS, normal-flow low-gradient severe AS.

proportion of TAVR in NF-LG-SAS in our study (n=16; 13%), we are not able to test the impact of this technique on outcomes in these patients. Unfortunately, the precise echocardiographic follow-up was not integrated in the design of this study, and further studies are needed to evaluate the progression of NF-LG-SAS and to define the optimal follow-up rhythm in these patients. In our study patients were followed by clinical consultations and echocardiography based on guidelines, generally each year for MAS (AVA 1-1.3 cm^2) and twice a year for NF-LG-SAS patients (AVA <1 cm^2). Although, we systematically use a careful methodology to eliminate any echocardiographic measurement errors, inherent measurement errors may have led to a certain degree of misclassification of MAS as NF-LG-SAS. We did not systematically perform additional examinations, such as transesophageal echocardiography or cardiac computed tomography to measure LVOT diameter. Moreover, in spite of our best efforts in measuring LVOT diameter using transthoracic echocardiography, its elliptical shape may have led to underestimation of the LVOT cross-sectional area and therefore AVA. However, the transthoracic echo-Doppler–derived stroke volume measurement, despite its limitations, remains part of any routine echocardiographic examination and, in patients with AS, is usually used to calculate the AVA. This study was an observational study, which implies that the 2 groups (Tables 1 and 2) comprised different patients, but in order to control the impact of these differences on outcome, we performed multivariate analyses and propensity score matching, and the results remain unchanged.

Clinical Implications

Our results show that patients with NF-LG-SAS should be considered as patients with MAS and managed as such. The key step is to rule out measurement errors during the initial echocardiography using a rigorous methodology and, when

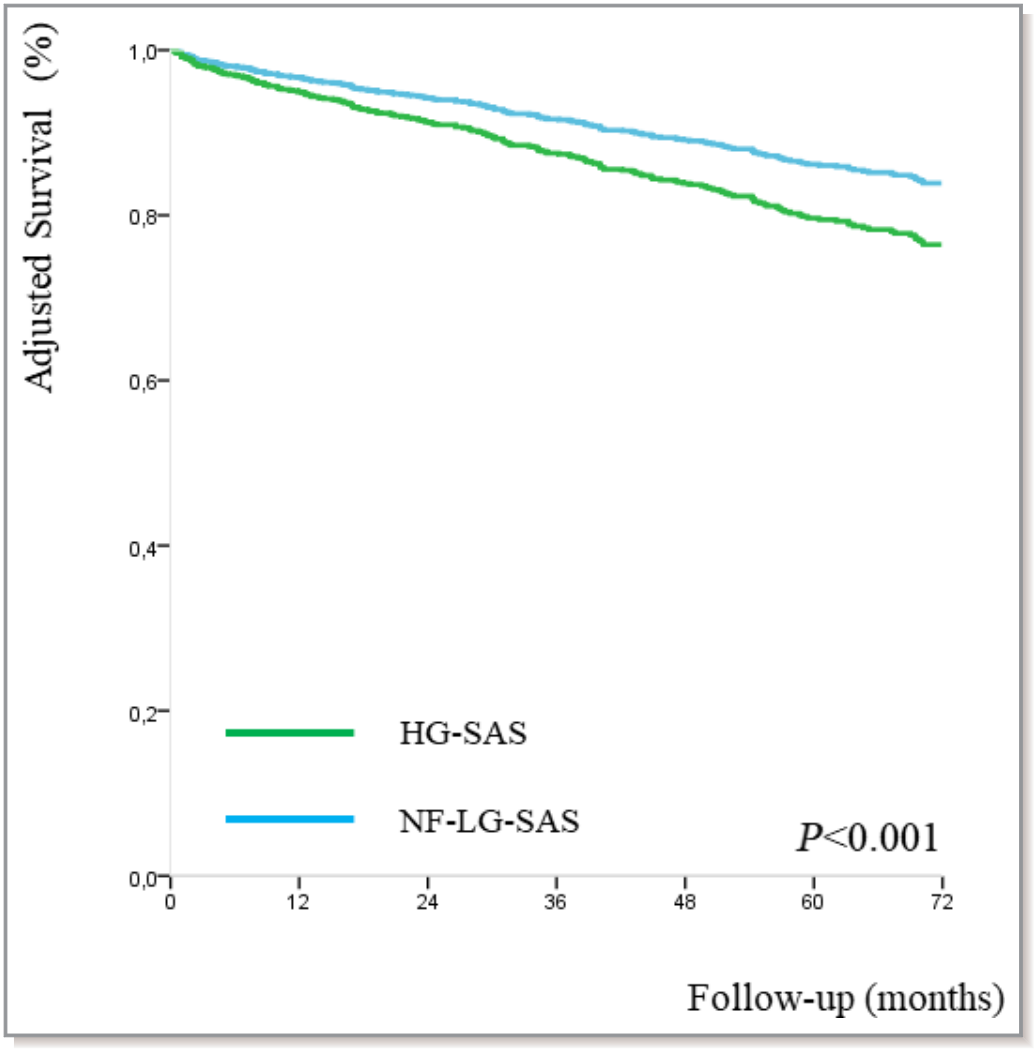

Figure 5. Adjusted survival curves under medical and surgical management according to the type of aortic stenosis (HG-SAS or NF-LG-SAS). AS indicates aortic stenosis; HG-SAS, high-gradient severe AS; NF-LG-SAS, normal-flow, low-gradient severe AS.

there is a doubt about the severity of AS, to perform additional examinations, notably multislice computed tomography to assess the calcium score, analyze the LVOT shape, and measure the anatomic AVA. When there is a persistent doubt concerning the severity of AS, cardiac catheterization should be performed if aortic valve replacement is discussed in order to verify the values of stroke volume, mean gradient, and AVA. In these patients, watchful observation with echocardiographic monitoring after the diagnosis is essential to detect progression to HG-SAS. Timely performance of AVR during follow-up should be considered as a therapeutic option for these patients. A randomized controlled trial is needed to precisely define the role and timing of AVR in NF-LG-SAS.

Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1. Comparison of baseline characteristics between normal-flow low-gradient severe aortic stenosis (NF-LG-SAS) and high gradient severe aortic stenosis (HG-SAS).

Variables	NF-LG-SAS (n=154)	HG-SAS (n=1055)	p value
Demographics, baseline data and symptoms			
Age (years)	79 ± 9	75 ± 11	**<0.001**
Male sex (n,%)	67 (43.5%)	539 (51.0%)	**0.029**
Body surface area (m²)	1.82 ± 0.2	1.86 ± 0.2	**0.010**
NYHA (n,%)			
I-II	129 (83.8%)	777 (73.6%)	**<0.001**
III-IV	25 (16.2%)	278 (26.4%)	
Medical history and risk factors			
Hypertension (n,%)	125 (81.2%)	765 (72.5%)	**0.041**
Diabetes mellitus (n,%)	47 (30.5%)	299 (28.3%)	0.23
Coronary artery disease (n, %)	79 (51.3%)	549 (52%)	0.21
Prior myocardial infarction (n,%)	14 (9.1%)	77 (7.3%)	0.12
Prior atrial fibrillation (n,%)	54 (35.1%)	295 (28.0%)	0.28
Charlson comorbidity index	2.06 ± 2.0	1.93 ± 1.9	0.32
Echocardiography and Doppler parameters			
Aortic valve			
Aortic valve area (cm²)	0.90 (0.82-0.97)	0.69 (0.58-0.80)	**<0.001**
Peak aortic jet velocity (m/s)	3.6 (3.3-3.8)	4.6 (4.3-5.1)	**<0.001**
Transaortic mean pressure gradient (mmHg)	32 (26-36)	53 (46-66)	**<0.001**
Dimensionless index	0.25 (0.22-0.27)	0.19 (0.16-0.22)	**<0.001**
Indexed stroke volume (ml/m²)	41 (38-45)	42 (35-48)	0.55
Left-sided heart evaluation			
LV end-diastolic diameter (mm)	48 (44-52)	49 (45-54)	**0.004**
LV end-systolic diameter (mm)	30 (26-33)	30 (26-35)	0.141
Ejection fraction (%)	65 (60-68)	64 (59-70)	0.26
Indexed LV mass (g/m²)	117 (99-147)	132 (107–158)	**<0.001**
Indexed left atrial volume (mL/m²)	42 (33-54)	41 (33-53)	0.68

Continuous normally distributed variables are expressed as mean ±1 standard deviation, non-normally distributed continuous variables are expressed as median (25th and 75th percentiles), and categorical variables as percentages and counts.

LV: Left Ventricular; HG-SAS: High gradient severe aortic stenosis, NYHA: New York Heart Association class, NF-LG-SAS: normal-flow low-gradient severe aortic stenosis