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ORIGINAL RESEARCH

Prognostic Implications of Discordant Low-Gradient Severe Aortic Stenosis

Comprehensive Analysis of a Large Multicenter Registry

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ABSTRACT

BACKGROUND Up-to-30% of patients with severe aortic stenosis (SAS) (indexed aortic valve area [AVAi] < 0.6 cm^2/m^2) exhibit low-transvalvular gradient despite normal ejection fraction. There is intense debate regarding the prognostic significance of this entity.

OBJECTIVE To compare the outcome of patients with discordant low-gradient SAS (DLG-SAS) vs moderate aortic stenosis (MAS) and high-gradient SAS (HG-SAS).

METHODS We used the BEL-F-ASt (Belgium-France-Aortic Stenosis) registry including consecutive patients with AS. Survival was compared overall and after matching (inverse probability weighting and propensity-score matching) for clinical and imaging variables. The analysis was first performed in the overall population (n = 2,582) and then in the population of unoperated patients (n = 1,812).

RESULTS After-inverse probability weighting-matching, the 3 groups were balanced. Five-year survival was better in MAS than in DLG-SAS and HG-SAS-patients (58.9% vs 47% vs 41.2%, $P < 0.001$). Similar results were obtained in unoperated patients (54.1% vs 37.9% vs 28.1%, $P < 0.001$). To explore the impact of MG (≤40 vs >40 mmHg) and AVAi (<0.6 vs ≥0.6 cm^2/m^2) on outcomes, survival of propensity score-matched cohorts of HG-vs DLG-SAS and MAS vs DLG-SAS were compared. After matching for MG, survival was better in MAS than in DLG-SAS (52% vs 40%, $P < 0.001$). After matching for AVAi, survival was better in DLG-SAS than in HG-SAS patients (45% vs 33%, $P < 0.001$).

CONCLUSIONS Survival of DLG-SAS is better than that of HG-SAS and worse than that of MAS patients. At comparable MG, the lower the AVAi, the worse the prognosis, whereas at comparable AVAi, the higher the MG, the worse the prognosis. These data argue that DLG-SAS is an intermediate form in the disease continuum. (JACC Adv 2023;■:100254)

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ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis

AVA = aortic valve area

AVAi = indexed aortic valve area

AVR = aortic valve replacement

BSA = body surface area

CAD = coronary artery disease

DLG-SAS = discordant low-gradient severe aortic stenosis

HG-SAS = high-gradient severe aortic stenosis

IPW = inverse probability weighting

IQR = interquartile range

LV = left ventricular

LVEF = left ventricular ejection fraction

LVOT = left ventricular outflow track

MAS = moderate aortic stenosis

MG = mean gradient

SAS = severe aortic stenosis

SVi = indexed stroke volume

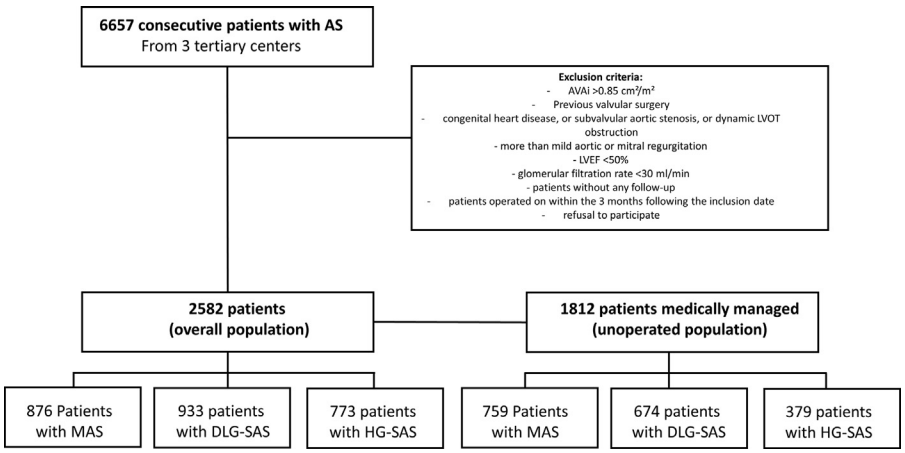
Aortic valve stenosis (AS) is the most prevalent valvular disease in the Western world, affecting more than 5% of patients aged over 65 years.[1] Echocardiography is the gold standard for assessing AS severity. Severe aortic stenosis (SAS) in its typical form, that is, high-gradient SAS (HG-SAS), is defined as an aortic valve area (AVA) <1.0 cm^2 or an indexed AVA (AVAi) <0.6 cm^2/m^2 and a mean gradient (MG) >40 mmHg.[2,3] However, 10 to 30% of patients present with discordant findings: lower-than-expected peak transvalvular velocities and mean pressure gradients (MG ≤ 40 mmHg) despite SAS based on AVAi (<0.6 cm^2/m^2). Since transvalvular pressure gradients are flow-dependent, it has long been admitted that patients with left ventricular (LV) dysfunction and low cardiac output may present with low MG despite SAS.[4] More recently, retrospective studies have shown that such low transvalvular gradients can also be observed in patients with preserved LV ejection fraction (LVEF),[5,6] presumably as a result of small cavity sizes and low stroke volumes, typically <35 mL/m^2. Because it is observed in patients with normal LVEF, this subset of SAS has been termed "discordant low-gradient" (DLG-SAS). Clearly, this situation raises uncertainty regarding the actual severity of the stenosis, prognostic implications, and therapeutic management. Indeed, some authors consider this entity as a more advanced form of AS,[7] with increased interstitial fibrosis,[8] reduced LV longitudinal function,[9] and poor prognosis under conservative treatment,[10] while others provided evidence that it is a more benign form of AS, with an outcome similar to that of moderate AS (MAS).[11,12] In addition, it has been found out that DLG-SAS patients are "en route" toward the more severe HG-SAS, since the majority of them experience a MG increase over time.[12] Consistently, magnetic resonance imaging data in DLG-SAS show larger AVAs, less hypertrophy, and similar focal fibrosis compared to HG-SAS.[13] Survival analyses of limited patient numbers suggest that DLG-SAS is associated with a greater mortality risk than HG-SAS,[10] while it was more recently shown that the outcome of DLG-SAS was similar to that of MAS and was not favorably influenced by aortic valve surgery.[11,14] All these conflicting data raise questions about the real severity of DLG-SAS, and a better comprehension of this particular entity should help clinicians in making appropriate therapeutic decisions. Indeed, current guidelines mention that treatment may be considered in symptomatic patients with DLG-SAS, but only as a class IIa indication (level of evidence C), which reflects the uncertainty as to treatment survival benefit.[2]

In view of these controversies and given the lack of randomized trials, the only option for refining the prognostic implication of DLG-SAS is to gather registries of patients with SAS and to compare the outcome after matching baseline characteristics. In this work, we gathered large and well-defined AS registries (treated and untreated patients) in France and Belgium and hypothesized that DLG-SAS represents an intermediate form of AS in the disease continuum, between MAS and HG-SAS. By censoring patients at the time of surgery, we sought to minimize the effects on outcome of treatment and of its potentially heterogeneous use in the 3 groups.

METHODS

STUDY POPULATION AND DESIGN. Patients aged 18 years and older, who were diagnosed with at least mild AS in the echocardiography laboratories of 2 French (Amiens and Lille) and one Belgian (Brussels) tertiary hospitals between 2000 and 2020, were prospectively enrolled and entered in an electronic database (**Figure 1**). Exclusion criteria were as follows: 1) AVAi >0.85 cm^2/m^2, 2) previous valvular surgery, congenital heart disease, subvalvular aortic stenosis, or dynamic LV outflow tract (LVOT) obstruction, 3) more than mild aortic or mitral regurgitation, 4) LVEF <50%, 5) glomerular filtration rate <30 mL/min, 6) patients without any follow-up (inclusion date = last follow-up date), 7) patients operated on within the first 3 months following the inclusion date, and 8) refusal to participate in the study. Overall, we enrolled 2,582 patients of which 1,812 were medically managed. The patients were retrospectively classified into 3 groups: MAS (AVAi ≥ 0.6 cm^2/m^2, MG ≤ 40 mmHg, n = 876), DLG-SAS (AVAi < 0.6 cm^2/m^2, MG ≤ 40 mmHg, n = 933), and HG-SAS (MG ≥ 40 mmHg, AVAi < 0.6 cm^2/m^2, n = 773). The validated Charlson comorbidity index was calculated for each patient.[15] Coronary artery disease (CAD) was defined as the presence of a documented history of acute coronary syndrome, CAD previously confirmed by coronary angiography, or history of coronary revascularization. Symptoms were ascertained by each patient's personal cardiologist and graded according to the New York

FIGURE 1 Flow Chart Illustrating Case Selection and Classification



AVAi = indexed aortic valve area; DLG-SAS = discordant low-gradient severe aortic stenosis; HG-SAS = high-gradient severe aortic stenosis; LVEF = left ventricular ejection fraction; MAS = moderate aortic stenosis.

Heart association (NYHA). The study was conducted in accordance with institutional policies and the revised Helsinki Declaration.

ECHOCARDIOGRAPHY. All patients underwent a comprehensive ultrasound examination using commercially available systems, including 2-dimensional echocardiography as well as Doppler examinations. Multiple transducer positions were systematically used to record maximal instantaneous and mean pressure gradients across the aortic valve. AVA was calculated by the continuity equation and indexed for body surface area (BSA). In patients with atrial fibrillation, 5 consecutive beats were systematically averaged. LV volumes and LVEF were calculated by using the biplane Simpson method. LV stroke volume was calculated by means of the LVOT area on the parasternal long-axis view multiplied by the LVOT velocity-time integral measured by pulsed-wave Doppler. Systolic pulmonary artery pressure was estimated by measuring the systolic transtricuspid pressure gradient, as calculated using the modified Bernoulli equation.

FOLLOW-UP AND OUTCOME. As previously reported,[16] initial treatment after the index evaluation was either conservative or surgical, as judged appropriate by the patient's cardiologist. Subsequent clinical decisions about surgical management (aortic valve replacement [AVR]) were made by the heart team with the approval of the patient's personal physician, as per guidelines. Clinical follow-up data were obtained by direct patient interview and telephone calls to physicians, patients, or their relatives if necessary. Follow-up started at the time of the index echocardiography, and patients undergoing AVR during follow-up were censored at the time of surgery. The study endpoint was overall mortality.

STATISTICAL ANALYSIS. Continuous data are expressed as mean ± standard deviation or median and interquartile range [IQR], depending on distribution normality. Categorical data are expressed as number and percentage. The differences in baseline continuous data among the 3 groups were explored using one-way analysis of variance (for normally distributed data) or Kruskal-Wallis test (for non-normally distributed data). Pearson's chi-squared test was used for categorical variables. Outcomes are displayed using the Kaplan-Meier method and were compared using 2-sided log-rank tests. Multivariable analyses of all-cause mortality were performed using Cox proportional hazards models adjusted for baseline characteristics. In order to avoid bias related to surgical treatment, these analyses were conducted both on the overall population of 2,512 patients and on the specific population of 1,812 unoperated patients. To adjust for covariates between groups (MAS, DLG-SAS, and HG-SAS), a propensity score inverse probability weighting (IPW) estimation was computed for each patient. All baseline characteristics that were significantly different between groups with a prognostic impact in multivariate analysis by Cox survival model (Tables 1 and 2) were used to calculate the propensity score IPW for each

TABLE 1 Baseline and Inverse Probability Weighting (IPW)-Weighted Characteristics of the Overall Population

	Overall Population (n = 2,582)				IPW Population			
	MAS N = 876	DLG-SAS N = 933	HG-SAS N = 773	*P*-Value	MAS N = 876	DLG-SAS N = 933	HG-SAS N = 773	*P*-Value
Clinical data								
Male sex (n, %)	468 (53.4)	454 (48.7)	400 (51.7)	0.12	50.9%	50.5%	51.2%	0.97
Age (y)	76 ± 11	77 ± 11	76 ± 12	0.001	76 ± 11	77 ± 11	77 ± 11	0.88
BMI (kg/m^2)	27 ± 5	28 ± 6	28 ± 5	0.001	28 ± 6	28 ± 5	28 ± 5	0.60
BSA (m^2)	1.9 ± 0.2	1.9 ± 0.2	1.9 ± 0.2	0.002	1.9 ± 0.2	1.9 ± 0.2	1.9 ± 0.2	0.90
NYHA I/II (n, %)	796 (91)	735 (78.8)	584 (75.5)	<0.001	80.1%	81.4%	81.8%	0.81
Angina (n, %)	121 (13.8)	131 (14.0)	129 (16.7)	0.19	14.7%	13.5%	15.5%	0.68
Syncope (n, %)	56 (6.4)	54 (5.8)	61 (7.9)	0.21	5.5%	5.9%	8.6%	0.16
Diabetes (n, %)	273 (31.2)	314 (33.7)	206 (26.6)	0.007	31.4%	31%	31.1%	0.99
Hypertension (n, %)	658 (75.1)	722 (77.4)	561 (72.6)	0.073	74.9%	75.6%	73.2%	0.72
CAD (n, %)	279 (31.8)	305 (32.7)	285 (36.9)	0.073	34.2%	33.1%	35.9%	0.69
AF (n, %)	265 (30.3)	324 (34.7)	192 (24.8)	<0.001	31.1%	29.4%	32.1%	0.70
Charlson index (%)	4.7 ± 2.3	4.8 ± 2.2	4.7 ± 2.2	0.46	4.9 ± 2.3	4.7 ± 2.2	4.8 ± 2.3	0.25
GFR (mL/s)	67 ± 31	66 ± 28	67 ± 29	0.39	67 ± 32	66 ± 28	67 ± 29	0.78
Echocardiographic data								
AVA (cm^2)	1.3 ± 0.2	0.9 ± 0.2	0.7 ± 0.2	<0.001	1.3 ± 0.2	0.9 ± 0.2	0.7 ± 0.2	<0.001
AVAi (cm^2/m^2)	0.70 ± 0.07	0.48 ± 0.08	0.39 ± 0.09	<0.001	0.69 ± 0.07	0.49 ± 0.08	0.39 ± 0.09	<0.001
MG (mmHg)	20 ± 8	27 ± 8	5 ± 13	<0.001	20 ± 8	28 ± 7	53 ± 13	<0.001
Vmax (cm/s)	2.9 ± 0.5	3.3 ± 0.5	4.6 ± 0.5	<0.001	2.9 ± 0.5	3.4 ± 0.5	4.6 ± 0.5	<0.001
Svi < 35 mL/m^2 (n, %)	161 (18.4)	442 (47.4)	189 (24.5)	<0.001	29.9%	30.7%	29.5%	0.93
sPAP (mmHg)	34 ± 11	35 ± 12	35 ± 11	0.28	35 ± 13	34 ± 12	35 ± 11	0.60
sPAP ≥ 45 mmHg (n,%)	73 (8.3)	117 (12.5)	98 (12.7)	0.005	10.9%	10.9%	11.3%	0.98
EF (%)	64 ± 7	63 ± 8	63 ± 7	0.001	64 ± 8	64 ± 7	63 ± 7	0.67
AR2 (n, %)	22 (2.5)	22 (2.4)	40 (5.2)	0.002	3.2%	3.4%	3.4%	0.98

AF = atrial fibrillation; AR2 = aortic regurgitation grade 2; AVA = aortic valve area; AVAi = indexed aortic valve area; BMI = body mass index; BSA = body surface area; CAD = coronary artery disease; DLG-SAS = discordant low-gradient severe aortic stenosis; EF = ejection fraction; GFR = glomerular filtration rate; HG-SAS = high-gradient severe aortic stenosis; MAS = moderate aortic stenosis;MG = mean gradient; sPAP = systolic pulmonary artery pressure; Svi = indexed stroke volume; Vmax = maximal transvalvular velocity.

patient. The 5-year overall survival, computed using the Kaplan-Meier method adjusted for inverse probability weights, was then determined in order to clarify the impact of AS groups. Weighted groups were compared using log-rank chi-squared tests. The proportional hazards assumption was confirmed using statistics and graphs based on Schoenfeld residuals.

Finally, to explore the impact of MG (≤40 mmHg vs >40 mmHg) in patients with an AVAi <0.6 cm^2/m^2 (DLG-SAS vs HG-SAS) and of AVAi (<0.6 cm^2/m^2 vs ≥0.6 cm^2/m^2) in patients with a MG ≤ 40 mmHg (DLG-SAS vs MAS), we performed 2 different propensity score matching analyses. First, we added the MG to clinical variables for generating a propensity score for each patient with an AVAi <0.6 cm^2/m^2. Matched patient pairs (DLG-SAS vs HG-SAS) were then compared and 5-year overall survival analysis using the Kaplan-Meier method was carried out. Secondly, we added the AVAi to clinical variables for generating a propensity score for each patient with a MG ≤40 mmHg. Survival of matched patient pairs (MAS vs DLG-SAS) was compared as well. Propensity score matching was performed separately in the overall population and in the population of unoperated patients. All statistical analyses were conducted using the RStudio 1.4.1106 (ipw and weights packages)[17] and the SPSS version 27.0 (IBM Corp, Armonk, NY) software. A *P*-value of <0.05 was considered statistically significant.

RESULTS

BASELINE CHARACTERISTICS. The overall population consisted of 2,582 patients, of which 876 (34%) presented with MAS, 933 (36%) with DLG-SAS, and 773 (30%) with HG-SAS (Table 1). DLG-SAS patients were older and more frequently had diabetes and atrial fibrillation, as well as lowered stroke volume index and increased systolic pulmonary arterial pressure. MAS patients were less often in NYHA class >2 and had the highest LVEF. HG-SAS patients had

TABLE 2 Baseline and Inverse Probability Weighting (IPW)-Weighted Characteristics of the Unoperated Population

	Unoperated Population (n = 1,812 Patients)				IPW Population			
	MAS N = 759	DLG-SAS N = 674	HG-SAS N = 379	*P*-Value	MAS N = 759	DLG-SAS N = 674	HG-SAS N = 379	*P*-Value
Clinical data								
Male sex (n, %)	404 (53.2)	298 (44.2)	181 (47.8)	0.003	48.4%	47.2%	48.6%	0.94
Age (y)	76 ± 11	80 ± 10	80 ± 9	<0.001	78 ± 10	79 ± 10	79 ± 10	0.82
BMI (kg/m^2)	27 ± 5	28 ± 6	27 ± 5	0.002	28 ± 6	27 ± 5	27 ± 6	0.49
BSA (m^2)	1.9 ± 0.2	1.9 ± 0.2	1.8 ± 0.2	0.009	1.9 ± 0.2	1.9 ± 0.2	1.9 ± 0.2	0.84
NYHA I/II (n, %)	690 (90.9)	527 (78.2)	275 (72.6)	<0.001	82.1%	82.2%	81.2%	0.96
Angina (n, %)	105 (13.8)	89 (13.2)	63 (16.6)	0.29	14.7%	12.4%	14.1%	0.65
Syncope (n, %)	47 (6.2)	43 (6.4)	43 (11.3)	0.003	5.6%	6.5%	11.9%	0.017
Diabetes (n, %)	233 (30.7)	235 (34.9)	95 (25.1)	0.004	32.2%	31.7%	31.6%	0.99
Hypertension (n, %)	567 (74.7)	527 (78.2)	278 (73.4)	0.15	75%	76.1%	72.6%	0.67
CAD (n, %)	218 (28.7)	193 (28.6)	107 (28.2)	0.99	30%	28.5%	26.8%	0.73
AF (n, %)	235 (31.0)	257 (38.1)	112 (29.6)	0.003	33.8%	33%	37.3%	0.58
Charlson score (%)	4.9 ± 2.3	5.1 ± 2.2	5.1 ± 2.1	0.11	5.1 ± 2.2	4.9 ± 2.2	5.0 ± 2.3	0.46
GFR (mL/s)	66 ± 32	63 ± 28	61 ± 26	0.018	63 ± 30	63 ± 27	64 ± 28	0.77
Echocardiographic data								
AVA (cm^2)	1.3 ± 0.2	0.9 ± 0.2	0.7 ± 0.2	<0.001	1.3 ± 0.2	0.9 ± 0.2	0.7 ± 0.2	<0.001
AVAi (cm^2/m^2)	0.70 ± 0.07	0.48 ± 0.08	0.39 ± 0.09	<0.001	0.70 ± 0.07	0.5 ± 0.08	0.39 ± 0.09	<0.001
MG (mmHg)	20 ± 8	26 ± 8	53 ± 13	<0.001	19 ± 8	27 ± 7	53 ± 12	<0.001
Vmax (cm/s)	2.9 ± 0.5	3.3 ± 0.5	4.6 ± 0.5	<0.001	2.8 ± 0.5	3.3 ± 0.5	4.6 ± 0.5	<0.001
Svi < 35 mL/m^2 (n, %)	142 (18.7)	340 (50.4)	102 (26.9)	<0.001	30.8%	32.6%	31.2%	0.87
sPAP (mmHg)	34 ± 11	36 ± 13	36 ± 12	0.039	36 ± 13	35 ± 12	36 ± 11	0.77
sPAP ≥ 45 mmHg (n,%)	65 (8.6)	88 (13.1)	54 (14.2)	0.004	10.8%	11.3%	12.4%	0.86
EF (%)	64 ± 8	63 ± 8	62 ± 7	<0.001	64 ± 8	64 ± 7	63 ± 7	0.69
AR2 (n, %)	18 (2.4)	17 (2.5)	23 (6.1)	0.002	3.2%	3.3%	3.4%	0.98

AF = atrial fibrillation; AR2 = aortic regurgitation grade 2; AVA = aortic valve area; AVAi = indexed aortic valve area; BMI = body mass index; BSA = body surface area; CAD = coronary artery disease; DLG-SAS = discordant low-gradient severe aortic stenosis; EF = ejection fraction; GFR = glomerular filtration rate; HG-SAS = high-gradient severe aortic stenosis; MAS = moderate aortic stenosis;MG = mean gradient; sPAP = systolic pulmonary artery pressure; Svi = indexed stroke volume; Vmax = maximal transvalvular velocity.

more severe symptoms according to NYHA classification and more often grade 2 aortic regurgitation. There was no significant difference between groups in other clinical parameters, such as sex, angina, syncope, hypertension, and CAD. The Charlson comorbidity index was similar between the 3 groups. After IPW, no significant difference in baseline characteristics persisted (Table 1, right column). The unoperated population consisted of 1,812 patients distributed as follows: 759 (42%) with MAS, 674 (37%) with DLG-SAS, and 379 (21%) with HG-SAS (Table 2). Overall, these patients shared clinical and imaging characteristics similar to those of the overall population. Noteworthy, there were more women in the DLG-SAS group. As for the overall population, after IPW, no significant difference in baseline characteristics persisted (Table 2, right column).

PREDICTORS OF OUTCOME AND SURVIVAL IN THE THREE AORTIC STENOSIS GROUPS. For the overall population, a multivariate model was built with 9 covariates (age, sex, BSA, NYHA functional class, diabetes mellitus status, atrial fibrillation history, Charlson comorbidity index, systolic pulmonary artery pressure >45 mmHg, and indexed stroke volume (SVi), Table 3), while for the unoperated population, 7 covariates (age, BSA, NYHA functional class, atrial fibrillation history, Charlson comorbidity index, systolic pulmonary artery pressure >45 mmHg, and SVi, Table 4) were considered according to the parameters of univariate analysis. The echocardiographic parameters used for stratification of our groups (ie, AVAi and MG) were added separately to the multivariate model, and were both independently associated with survival for both the overall population (HR = 0.33, [0.2-0.55] 95% CI, *P*-value <0.001 for AVAi; HR = 1.05, [1.03-1.08] 95%CI; *P*-value <0.001 for MG) and the unoperated population (HR = 0.2, [0.12-0.33] 95%CI; *P*-value <0.001 for AVAi; HR = 1.07, [1.05-1.10]; *P*-value <0.001 for MG). During a median follow-up of 37.6 (IQR: 17.02) months, there were 770 AVRs and 1,003 deaths in the overall population.

TABLE 3 Univariate and Multivariate Analysis of 5-Year All-Cause Mortality in the Overall Population

	Univariate Analysis		Multivariate Analysis	
	HR [95% CI]	*P*-Value	HR [95% CI]	*P*-Value
Male sex	0.85 [0.74;0.97]	0.016	1.27 [1.08;1.49]	0.004
Age by 5 y	1.37 [1.32;1.43]	<0.001	1.26 [1.20;1.33]	<0.001
BMI	0.96 [0.94;0.97]	<0.001		
BSA	0.37 [0.28;0.51]	<0.001	0.50 [0.34;0.73]	<0.001
NYHA (I, II, III, IV)	1.46 [1.35;1.57]	<0.001	1.30 [1.20;1.40]	<0.001
Angina	0.91 [0.75;1.1]	0.34		
Syncope	1.19 [0.93;1.52]	0.17		
Diabetes	1.17 [1.02;1.36]	0.03	1.19 [1.02;1.39]	0.026
Hypertension	0.92 [0.79;1.08]	0.32		
CAD	0.99 [0.86;1.15]	0.89		
AF	1.80 [1.57;2.07]	<0.001	1.33 [1.15;1.53]	<0.001
Charlson index	1.20 [1.17;1.24]	<0.001	1.08 [1.04;1.12]	<0.001
GFR (Cockroft) by 5 mL/min	0.92 [0.90;0.93]	<0.001		
AVA	0.30 [0.24;0.38]	<0.001		
AVAi	0.14 [0.09;0.23]	<0.001		
MG by 5 mmHg	1.06 [1.04;1.09]	<0.001		
Vmax	1.28 [1.18;1.38]	<0.001		
sPAP ≥ 45 mmHg	1.82 [1.51;2.20]	<0.001	1.26 [1.03;1.53]	0.023
EF by 5%	0.91 [0.87;0.95]	<0.001		
Svi by 5 mL/m^2	0.92 [0.89;0.95]	<0.001	0.94 [0.91;0.98]	0.001
AR2	1.50 [1.04;2.16]	0.03		

AF = atrial fibrillation; AR2 = aortic regurgitation grade 2; AVA = aortic valve area; AVAi = indexed aortic valve area; BMI = body mass index; BSA = body surface area; CAD = coronary artery disease; EF = ejection fraction; GFR = glomerular filtration rate; MG = mean gradient; sPAP = systolic pulmonary artery pressure; Svi = indexed stroke volume; Vmax = maximal transvalvular velocity.

Unsurprisingly, the HG-SAS group had the highest surgery rate (51% vs 27.8% vs 13.4% for DLG-SAS and MAS, respectively; $P < 0.001$). Survival in the overall cohort at 1, 3, and 5 years was 87%, 67.2%, and 50.6%, respectively. Five-year survival differed markedly according to AS groups. IPW-adjusted survival was worst for HG-SAS, intermediate for DLG-SAS, and best for MAS (41.2% vs 47% vs 58.9%, respectively; $P < 0.001$, Figure 2A). In the unoperated population, the median follow-up was 27.6 (IQR: 40.6) months. As for the overall population, but even more pronounced, 5-year IPW-adjusted survival was worst for HG-SAS, intermediate for DLG-SAS, and best for MAS (28.1% vs 37.9% vs 54.1%, respectively; $P < 0.001$, Figure 2B). When considering MAS as the reference group, the increased relative risk for mortality was 29% in the DLG-SAS group and 58% in the HG-SAS group for the entire patient cohort. A similar finding was observed in the unoperated population (40% relative risk in the DLG-SAS group and 88% relative risk in the HG-SAS group). When stratified according to SVi (<35 mL/m^2 vs >35 mL/m^2), no difference in survival could be demonstrated into the DLG-SAS group ($P = 0.16$).

PROGNOSTIC IMPACT OF MEAN GRADIENT. All patients with an AVAi <0.6 cm^2/m^2 (DLG-SAS vs HG-SAS patients) were selected and matched according to relevant clinical baseline characteristics, except for the transvalvular gradient (Supplemental Table 1). The analysis was carried out in the overall population (377 pairs) and in the unoperated population (193 pairs). The 5-year overall survival analysis using the Kaplan-Meier method on pairs of matched patients showed a better survival for DLG-SAS patients compared to HG-SAS patients (Figure 3), both in the overall population (45% vs 33%, respectively; *P*-value <0.001, Figure 3A) and in the unoperated population (36% vs 27%, respectively; *P*-value <0.002, Figure 3B). Taken together, these data demonstrate that for a comparable AVAi, the higher the MG, the worse the prognosis.

PROGNOSTIC IMPACT OF AORTIC VALVE AREA. All patients with a MG ≤40 mmHg (MAS vs DLG-SAS patients) were selected and matched according to relevant clinical baseline characteristics, except for the AVA (Supplemental Table 2). The analysis was carried out in the overall population (448 pairs) and in the unoperated population (356 pairs). The 5-year overall survival analysis using the Kaplan-Meier method on pairs of matched patients showed a better survival for MAS patients compared to DLG-SAS patients (Figure 4), both in the overall population (52% vs 40%, respectively; *P*-value <0.001, Figure 4A) and in the unoperated population (46% vs 37%, respectively; *P*-value <0.001, Figure 4B). Taken together, these data demonstrate that for a comparable MG, the smaller the calculated AVAi, the worse the prognosis.

DISCUSSION

Our study evaluated the prognostic significance of DLG-SAS in a large, multicenter cohort of consecutive patients with AS. We compared the outcomes of this specific population with those of patients with MAS and HG-SAS. After a comprehensive adjustment for clinical variables, the prognosis of DLG-SAS patients was intermediate compared to that of MAS and HG-SAS patients. At comparable MG, that is, when MAS patients were matched with DLG-SAS patients for the main clinical characteristics, the prognosis of patients was clearly dependent on valve area. The smaller the valve area, the worse the prognosis. Conversely, at

comparable AVAi, that is, when DLG-SAS patients were matched with HG-SAS patients for the main clinical characteristics, the prognosis of patients depended on pressure gradient. The higher the gradient, the worse the prognosis.

These findings remained consistent, regardless of whether a global population of AS patients (censored at the time of surgery) or a specific population of unoperated patients was considered.

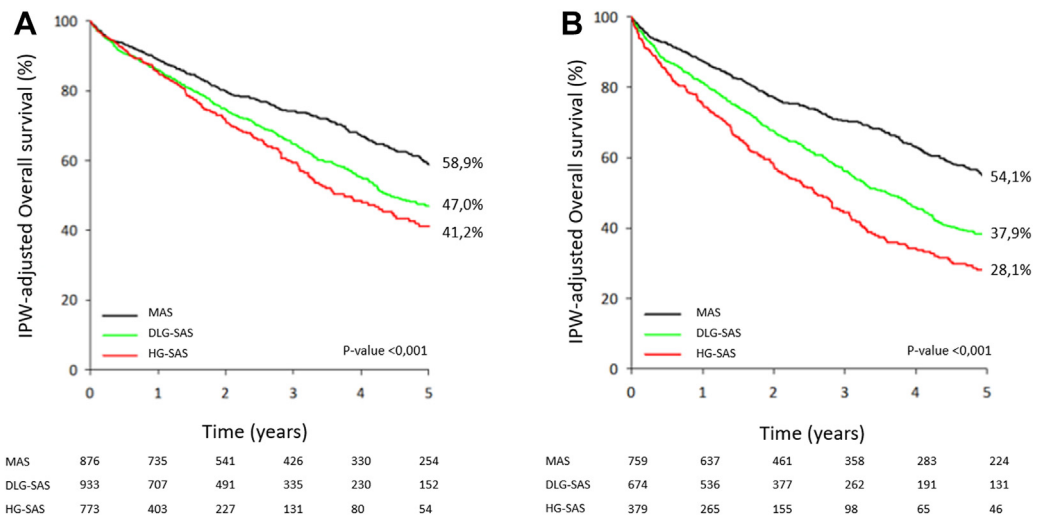
One of the strengths of this work is the number of patients, allowing us to adjust for potentially important confounders, such as age, body mass index, NYHA status, CAD, Charlson score, atrial fibrillation, renal function, and ejection fraction. Indeed, unlike other studies that explored the prognosis of patients with AS,[5,7] our IPW analysis and propensity matching analysis allowed us to control for all the clinical differences between our 3 groups and to identify the prognostic implication exclusively related to echocardiographic parameters such as MG and AVAi. Furthermore, we did not consider the need for AVR as an endpoint of our study so as to focus exclusively on a hard endpoint, that is, overall mortality. We also decided to perform our analysis on 2 different populations. First, after exclusion of patients operated on within the first 3 months after the index echocardiography, we analyzed a global population of patients, some of whom had undergone surgery during their

TABLE 4 Univariate and Multivariate Analysis of 5-Year All-Cause Mortality in the Unoperated Population

	Univariate Analysis		Multivariate Analysis	
	HR [95% CI]	*P*-Value	HR [95% CI]	*P*-Value
Male sex	0.94 [0.82;1.08]	0.40		
Age by 5 y	1.27 [1.22;1.32]	<0.001	1.15 [1.10;1.21]	**<0.001**
BMI	0.96 [0.95;0.98]	<0.001		
BSA	0.50 [0.37;0.68]	<0.001	0.71 [0.51;0.99]	**0.042**
NYHA (I, II, III, IV)	1.48 [1.38;1.58]	<0.001	1.33 [1.23;1.43]	**<0.001**
Angina	0.93 [0.77;1.12]	0.44		
Syncope	1.11 [0.87;1.42]	0.40		
Diabetes	1.18 [1.02;1.36]	0.027		
Hypertension	0.92 [0.78;1.07]	0.27		
CAD	1.17 [1.01;1.36]	0.03		
AF	1.63 [1.42;1.87]	<0.001	1.28 [1.12;1.48]	**0.001**
Charlson index	1.17 [1.14;1.20]	<0.001	1.10 [1.06;1.14]	**<0.001**
GFR (cockroft) by 5 mL/min	0.94 [0.92;0.95]	<0.001		
AVA	0.26 [0.20;0.33]	<0.001		
AVAi	0.09 [0.05;0.13]	<0.001		
MG by 5 mmHg	1.10 [1.08;1.12]	<0.001		
Vmax	1.45 [1.34;1.56]	<0.001		
sPAP ≥ 45 mmHg	1.75 [1.46;2.11]	<0.001	1.23 [1.01;1.49]	**0.042**
EF by 5%	0.91 [0.87;0.96]	<0.001		
Svi by 5 mL/m^2	0.93 [0.9;0.96]	0.001	0.96 [0.92;0.99]	**0.011**
AR2	1.52 [1.05;2.18]	0.026		

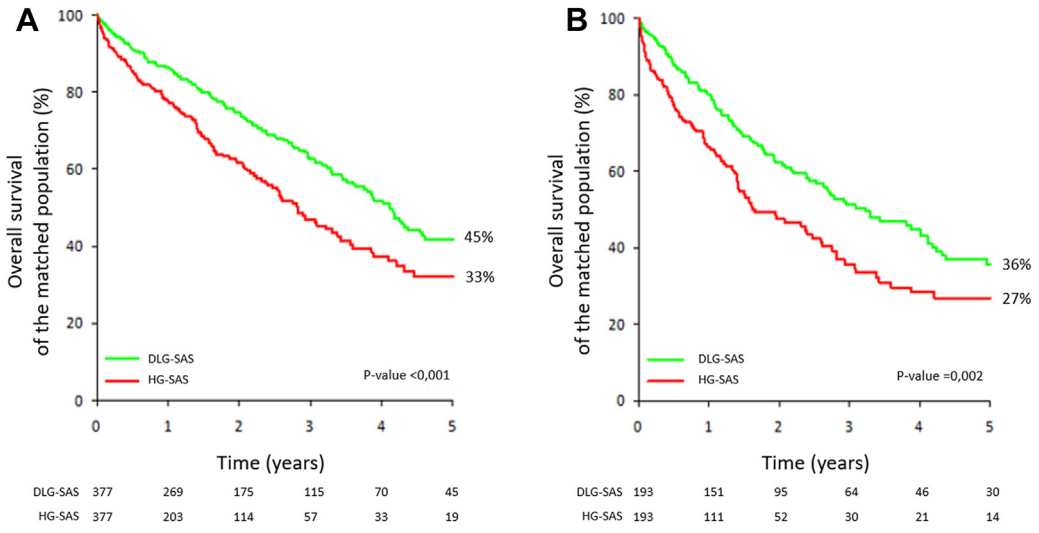
AF = atrial fibrillation; AR2 = aortic regurgitation grade 2; AVA = aortic valve area; AVAi = indexed aortic valve area; BMI = body mass index; BSA = body surface area; CAD = coronary artery disease; EF = ejection fraction; GFR = glomerular filtration rate; MG = mean gradient; sPAP = systolic pulmonary artery pressure; Svi = indexed stroke volume; Vmax = maximal transvalvular velocity.

FIGURE 2 Five-Year Inverse Probability Weighting-Adjusted Overall Survival Curves



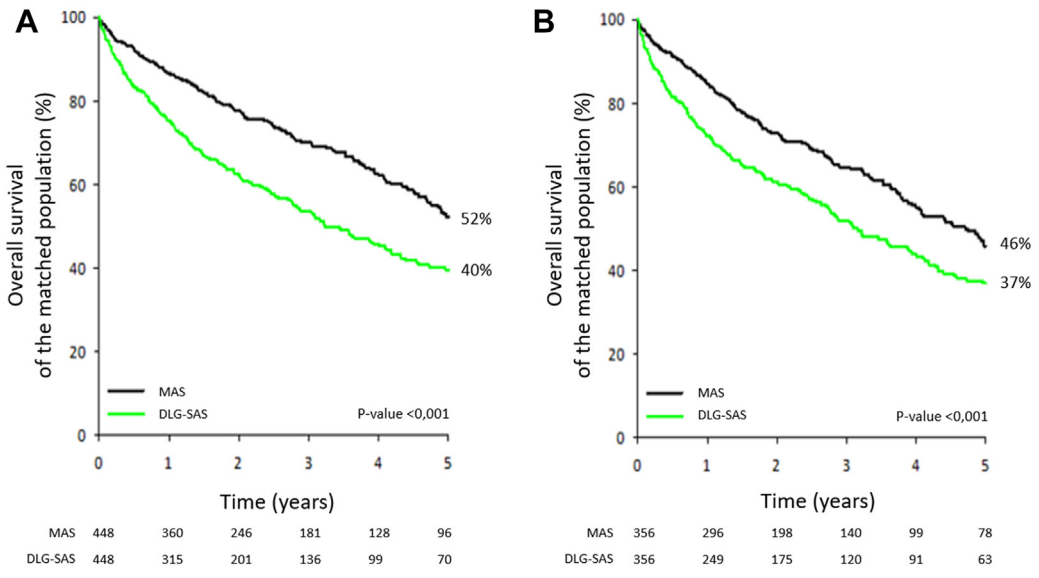
These curves compare survival among patients with MAS (black line), DLG-SAS (green line), and HG-SAS (red line) in the overall population **(A)** and in the unoperated population **(B)**. Numbers at bottom indicate patients at risk. DLG-SAS = discordant low-gradient severe aortic stenosis; HG-SAS = high-gradient severe aortic stenosis; IPW = inverse probability weighting; MAS = moderate aortic stenosis.

FIGURE 3 **Five-Year Overall Survival Analysis Comparing Pairs of Matched Patients With an AVAi <0.6 cm²/m²**



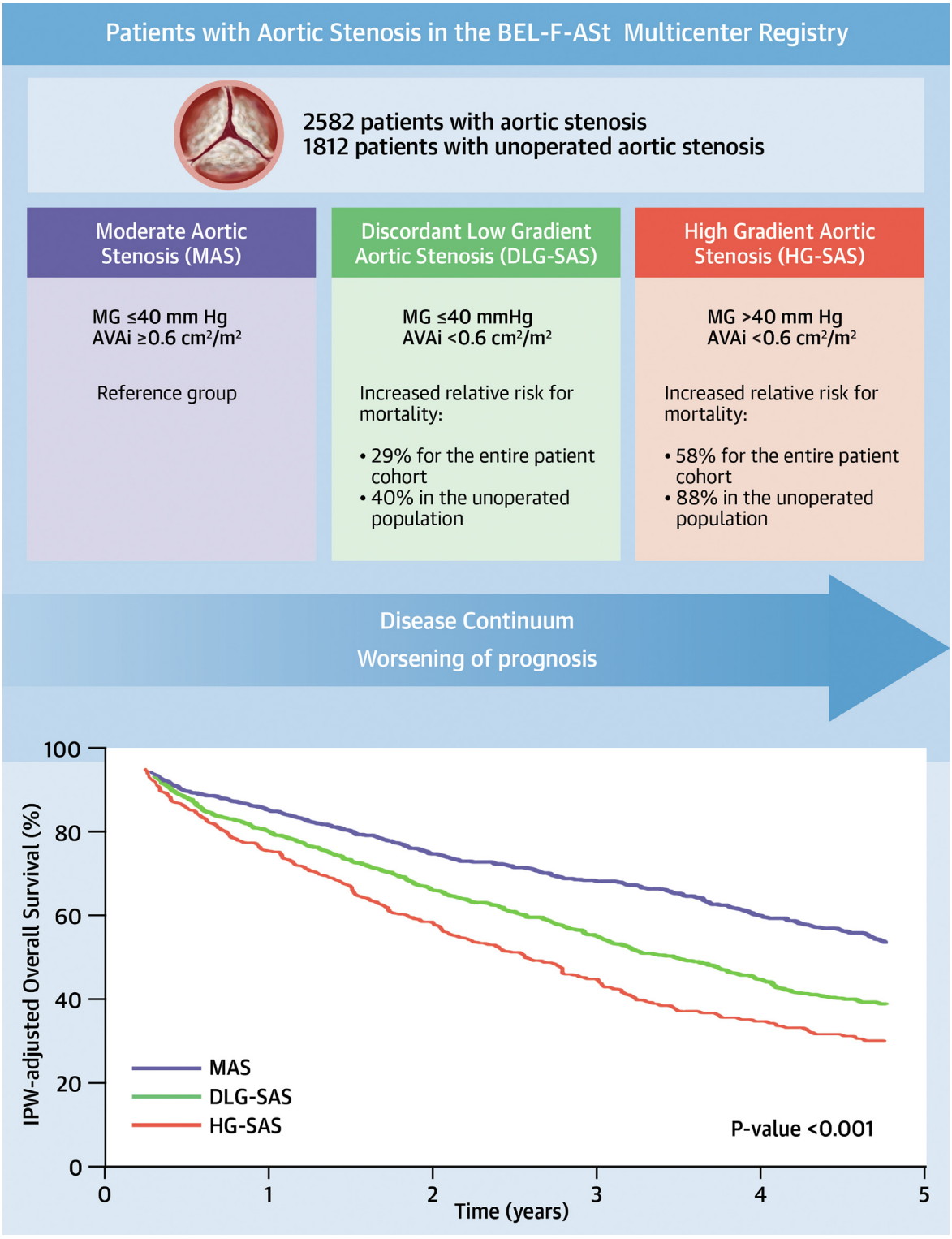
These curves show a better survival for patients with DLG-SAS (green line) compared to those with HG-SAS (red line) in the overall population **(A)** as well as in the unoperated population **(B)**. Numbers at bottom indicate patients at risk. AVAi = indexed aortic valve area; DLG-SAS = discordant low-gradient severe aortic stenosis; HG-SAS = high-gradient severe aortic stenosis.

FIGURE 4 **Five-Year Overall Survival Analysis Comparing Pairs of Matched Patients With a MG ≤40 mmHg**



These curves show a better survival for patients with MAS (black line) compared to those with DLG-SAS (green line) in the overall population **(A)** as well as in the unoperated population **(B)**. Numbers at bottom indicate patients at risk. DLG-SAS = discordant low-gradient severe aortic stenosis; MAS = moderate aortic stenosis.

CENTRAL ILLUSTRATION **The Disease Continuum of AS and the Prognostic Implications of the 3 Different Entities Classified According to MG and AVAi**



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clinical follow-up. Second, we analyzed a population of patients who had not undergone surgery in their clinical course, to avoid the bias related to AVR. Based on our data, we can state that DLG-SAS is an intermediate form in the AS disease continuum, between MAS and HG-SAS (**Central Illustration**).

CONTROVERSY AROUND THE CLINICAL SIGNIFICANCE OF DISCORDANT LOW GRADIENT SEVERE AORTIC STENOSIS. There is an intense debate about the clinical significance and particularly about the real severity of DLG-SAS. Some authors consider that DLG-SAS is a severe and advanced form of the disease that is associated with poor prognosis.[6,7,10] Others consider that it is a less severe form that can be safely monitored clinically.[11,12,14] Our study confirms that HG-SAS definitely has the worst prognosis when compared to MAS and DLG-SAS. A prospective study describing the natural history of MAS and DLG-SAS has shown that approximately 40% of patients progress to HG-SAS after a mean follow-up of 46 months.[14] This was subsequently confirmed by our research group.[12] These data provide a strong argument that DLG-SAS is a transient form of the disease evolving to a more severe form. Our data confirm this hypothesis from a strict prognostic perspective.

Low stroke volume has been proposed to be a major reason for a low transvalvular gradient in the presence of a normal ejection fraction and a potential cause for poorer prognosis.[5] Nevertheless, up to 50% of DLG-SAS patients have a normal stroke volume index, thereby highlighting that this parameter alone cannot explain the presence of low transvalvular gradient in case of an AVA <1 cm^2.[18] In our study, stroke volume was lower in the DLG-SAS group and low flow status was independently associated with overall mortality. Therefore it was incorporated in the propensity score. After adjustment for this parameter, the prognosis of DLG-SAS remained significantly worse than that of MAS and better than that of HG-SAS. Furthermore, as expected, patients with low flow DLG-SAS displayed a trend for a higher mortality risk compared with those with normal flow DLG-SAS, although not reaching the statistical significance ($P = 0.063$, Supplemental data, Figure 1). However, after adjustment of covariates, we could not find any difference in mortality risk between the 2 DLG-AS entities (HR: 1.18, 95% CI: 0.93-1.48), ($P = 0.167$, Supplemental data, Table). Our data are in line with the results of the prospective randomized SEAS (Simvastatin and Ezetimibe in Aortic Stenosis) study,[14] while they are discordant with the retrospective analysis of Eleid et al.[10] There are 2 potential explanations for these discrepancies. First, in the study by Eleid et al, the groups were not matched for important clinical variables and second, unindexed AVA was used to define AS severity groups, which may have resulted in larger differences in body mass index between groups and thus have contributed to differences in outcomes.

DISCORDANT LOW GRADIENT SEVERE AORTIC STENOSIS: A LESS MALIGNANT FORM OF AORTIC STENOSIS. Several factors may explain why DLG-SAS is an intermediate form of AS. When clinicians use the continuity equation or the Gorlin formula for assessing AS severity, they measure the size of the functional orifice instead of that of the anatomical orifice.[19] In its simplified form, it neglects the coefficient of orifice contraction, a factor that compensates for the continuous convergence of fluid streamlines beyond a narrowed orifice. Under physiological flow conditions, the degree of underestimation of the anatomical orifice by the continuity equation is expected to be approximately 10% to 15%. Furthermore, standard calculation of AVA determined by continuity equation requires 3 measurements: AS jet velocity, LVOT diameter, and LVOT velocity. However, while LVOT was traditionally assumed to be circular, recent studies have shown that LVOT is often elliptical, thus leading to LV stroke volume underestimation by another 10% to 15%.[20,21] This has major consequences on AS classification, resulting in significant inconsistencies in AS severity assessment. Indeed, many patients thought to have SAS when assuming that the LVOT is circular turn out to have only MAS. Furthermore, when measuring the anatomical AVA instead of the functional AVA, larger AVAs are observed in patients with DLG-SAS compared to those with HG-SAS.[13] In addition, DLG-SAS patients exhibit

CENTRAL ILLUSTRATION Continued

When considering MAS as the reference group, the increased relative risk for mortality is 29% in the DLG-SAS group and 58% in the HG-SAS group for the entire patient cohort. A similar finding is observed in the unoperated population (40% relative risk in the DLG-SAS group and 88% relative risk in the HG-SAS group). DLG-SAS is an intermediate form in the disease continuum, HG-SAS being definitely the most malignant AS form. AVAi = indexed aortic valve area; DLG-SAS = discordant low-gradient severe aortic stenosis; HG-SAS = high-gradient severe aortic stenosis; MAS = moderate aortic stenosis.

less hypertrophy and fibrosis when compared to HG-SAS patients.[22] Finally, it has been shown that DLG-SAS patients exhibit an aortic valve calcium load that is higher than that of MAS patients but lower than that of HG-SAS patients. Furthermore, although aortic valve calcium load was found to be predictive of DLG-SAS patient outcome, its prognostic impact is lower than in HG-SAS patients.[23] Taken together, these data clearly challenge the view that DLG-SAS is a more advanced form of AS.

IMPLICATIONS AND PERSPECTIVES. Treating DLG-SAS or even MAS may likely improve the patient prognosis because of the progressive nature of the disease. However, the patients who will benefit the most from treatment are obviously those with HG-SAS. Our data demonstrate that patients with DLG-SAS have a better prognosis than those with HG-SAS. Transcatheter AVR is increasingly proposed and is becoming the reference treatment even in low-surgical-risk patients. Yet, this treatment is associated with significant risks and high costs.[24] Therefore, it is essential not to offer potentially futile treatment to patients who can be safely followed up clinically. This is especially true in case of frailty, advanced age, and multiple comorbidities. Our data support this view. These patients must be meticulously selected by weighing the treatment against the natural prognosis of the disease. Randomized prospective studies are needed to clarify the benefit of AVR for patients with DLG-SAS and help clinicians in making therapeutic decisions. Finally, considering our data and in accordance with international guidelines,[2,3] the presence of a higher transvalvular gradient (ie, 30-40 mmHg vs 20-30 mmHg) and a smaller AVAi (ie, AVAi <0.45 cm^2/m^2 vs <0.6 cm^2/m^2) should guide clinicians in making treatment decisions in this particular DLG-SAS population.

LIMITATIONS. The study has several limitations that should be acknowledged. Because follow-up data were obtained retrospectively, this study presents the limitations inherent to this type of analysis. Our study exclusively concerned patients with preserved LVEF and without significant valve regurgitation and thus, the results cannot be extrapolated to patients with concomitant LV dysfunction or with complex multivalvular disease. Some variables previously reported as being risk factors for disease progression (ie, LV longitudinal strain, left atrial volume, B-type natriuretic peptide, and valve calcification) were not measured in this study, which limits the characterization of the different study groups. A substantial number of patients were included in the 2000s. The recommendations at this time did not encourage routine calcium score in DLG-SAS patients.

CONCLUSION

In this large multicenter cohort, survival of DLG-SAS patients was better than that of HG-SAS patients and worse than that of MAS patients. Furthermore, at comparable MG, the smaller the calculated AVAi, the worse the prognosis, while at comparable AVAi, the higher the MG, the worse the prognosis. Taken together, these data argue that DLG-SAS is an intermediate form in the disease continuum, HG-SAS being definitely the most malignant AS form. Prospective studies are needed to clarify the benefit of AVR for DLG-SAS patients and help clinicians in making appropriate therapeutic decisions for this specific AS population.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Survival of DLG-SAS patients is better than that of HG-SAS patients and worse than that of MAS patients. At comparable MG, the smaller the calculated AVAi, the worse the prognosis, while at comparable AVAi, the higher the MG, the worse the prognosis. Considering our data and in accordance with international guidelines, the presence of a higher transvalvular gradient (ie, 30-40 mmHg vs 20-30 mmHg) and a smaller AVAi (ie, AVAi <0.45 cm^2/m^2 vs <0.6 cm^2/m^2) should guide clinicians in making treatment decisions in this particular DLG-SAS population.

TRANSLATIONAL OUTLOOK: Prospective studies are needed to clarify the benefit of AVR for DLG-SAS patients.

REFERENCES

1. Virani SS, Alonso A, Benjamin EJ, et al. Heart disease and stroke statistics - 2020 update: a report from the American Heart Association. *Circulation*. 2020;141(9):e139–e596.

2. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Joint Committee on clinical practice guidelines. *Circulation*. 2021;143:e72–e227.

3. Vahanian A, Beyersdorf F, Praz F, et al. 2021 ESC/EACTS guidelines for the management of valvular heart disease. *Eur Heat J*. 2022;43(7):561–632.

4. Connolly HM, Oh JK, Shaff HV, et al. Severe aortic stenosis with low transvalvular gradient and severe left ventricular dysfunction. *Circulation*. 2000;101:1940–1946.

5. Hachicha Z, Dumesnil JG, Bogaty P, Pibarot P. Paradoxical low-flow, low-gradient severe aortic stenosis despite preserved ejection fraction is associated with higher afterload and reduced survival. *Circulation*. 2007;115:2856–2864.

6. Dumesnil JG, Pibarot P, Carabello B. Paradoxical low flow and/or low gradient severe aortic stenosis despite preserved left ventricular ejection fraction: implications for diagnosis and treatment. *Eur Heart J*. 2010;31:281–289.

7. Clavel M-A, Dumesnil JG, Capoulde R, Mathieu P, Sénéchal M, Pibarot P. Outcome of patients with aortic stenosis, small valve area, and low-flow, low-gradient despite preserved left ventricular ejection fraction. *J Am Coll Cardiol*. 2012;60:1259–1267.

8. Herrmann S, Störk S, Niemann M, et al. Low-gradient aortic valve stenosis myocardial fibrosis and its influence on function and outcome. *J Am Coll Cardiol*. 2011;58:402–412.

9. Adda J, Mielot C, Giorgi R, et al. Low-flow, low-gradient severe aortic stenosis despite normal ejection fraction is associated with severe left ventricular dysfunction as assessed by speckle-tracking echocardiography: a multicenter study. *Circ Cardiovasc Imaging*. 2012;5:27–35.

10. Eleid MF, Sorajja P, Michelena HI, Malouf JF, Scott CG, Pellika PA. Flow-gradient patterns in severe aortic stenosis with preserved ejection fraction. Clinical characteristics and predictors of survival. *Circulation*. 2013;128:1781–1789.

11. Tribouilloy C, Rusinaru D, Maréchaux S, et al. Low-gradient, low-flow severe aortic stenosis with preserved left ventricular ejection fraction: characteristics, outcome, and implications for surgery. *J Am Coll Cardiol*. 2015;65:55–66.

12. Maes F, Boulif J, Piérard S, et al. Natural history of paradoxical low-gradient severe aortic stenosis. *Circ Cardiovasc Imaging*. 2014;7:714–722.

13. Barone-Rochette G, Piérard S, Seldrum S, et al. Aortic valve area, stroke volume, left ventricular hypertrophy, remodeling, and fibrosis in aortic stenosis assessed by cardiac magnetic resonance imaging. Comparison between high and low gradient and normal and low flow aortic stenosis. *Circ Cardiovasc Imaging*. 2013;6:1009–1017.

14. Jander N, Minners J, Holme I, et al. Outcome of patients with low-gradient "severe" aortic stenosis and preserved ejection fraction. *Circulation*. 2011;123:887–895.

15. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40:373–383.

16. Maréchaux S, Rusinaru D, Altes A, Pasquet A, Vanoverschelde J-L, Tribouilloy C. Prognostic value of low flow in patients with high transvalvular gradient severe aortic stenosis and preserved left ventricular ejection fraction: a multicenter study. *Circ Cardiovasc Imaging*. 2019;12:e009299.

17. Van der Wal WM, Geskus RB. Ipw: an R package for inverse probability weighting. *J Stat Softw*. 2011;43:1–23.

18. Minners J, Allgeier M, Gohlke-Baerwolf C, Kienzle R-P, Neumann F-J, Jander N. Inconsistent grading of aortic valve stenosis by current guidelines: haemodynamic studies in patients with apparently normal left ventricular function. *Heart*. 2010;96:1463–1468.

19. Baumgartner H, Hung J, Bermejo J, et al. Recommendations on the echocardiographic assessment of aortic valve stenosis: a focused update from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. *Eur Heart J Cardiovasc Imaging*. 2017;18:254–275.

20. Maes F, Piérard S, de Meester C, et al. Impact of left ventricular outflow tract ellipticity on the grading of aortic stenosis in patients with normal ejection fraction. *J Cardiovasc Magn Reson*. 2017;19:37.

21. Michelena HI, Margaryan E, Miller FA, et al. Inconsistent echocardiographic grading of aortic stenosis: is the left ventricular outflow tract important? *Heart*. 2013;99:921–931.

22. Slimani A, Roy C, de Meester C, et al. Structural and functional correlates of gradients-area patterns in severe aortic stenosis and normal ejection fraction. *JACC Cardiovasc Imaging*. 2021;14:525–536.

23. Boulif J, Slimani A, Lazal S, et al. Diagnostic and prognostic accuracy of aortic valve calcium scoring in patients with moderate-to-severe aortic stenosis. *Front Cardiovasc Med*. 2021;8:673519.

24. Santarpino G, Lorusso R, Moscarelli M, et al. Stuturless versus transcatheter aortic valve replacement: a multicenter analysis of "real-world" data. *J Cardiol*. 2022;79:121–126.

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