

# Natural Progression of Low-Gradient Severe Aortic Stenosis with Preserved Ejection Fraction

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Because the natural progression of low-gradient aortic stenosis (LGAS) has not been well defined, we performed a retrospective study of 116 consecutive patients with aortic stenosis who had undergone follow-up echocardiography at a median interval of 698 days (range, 371–1,020 d). All patients had preserved left ventricular ejection fraction ( $>0.50$ ) during and after follow-up.

At baseline, patients were classified by aortic valve area (AVA) as having mild stenosis ( $\geq 1.5$  cm<sup>2</sup>), moderate stenosis ( $\geq 1$  to  $<1.5$  cm<sup>2</sup>), or severe stenosis ( $<1$  cm<sup>2</sup>). Severe aortic stenosis was further classified by mean gradient (LGAS, mean  $<40$  mmHg; high-gradient aortic stenosis [HGAS], mean  $\geq 40$  mmHg). We compared baseline and follow-up values among 4 groups: patients with mild stenosis, moderate stenosis, LGAS, and HGAS.

At baseline, 30 patients had mild stenosis, 54 had moderate stenosis, 24 had LGAS, and 8 had HGAS. Compared with the moderate group, the LGAS group had lower AVA but similar mean gradient. Yet the actuarial curves for progressing to HGAS were significantly different: 25% of patients in LGAS reached HGAS status significantly earlier than did 25% of patients in the moderate-AS group (713 vs 881 d;  $P=0.035$ ).

Because LGAS has a high propensity to progress to HGAS, we propose that low-gradient aortic stenosis patients be closely monitored as a distinct subgroup that warrants more frequent echocardiographic follow-up. (**Tex Heart Inst J 2014;41(3):273-9**)

**Key words:** Aortic valve stenosis; blood flow velocity; calcinosis/complications; disease progression; echocardiography; forecasting; prognosis; retrospective studies; risk assessment; stroke volume; time factors; ventricular function, left

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In the western world, aortic stenosis (AS) is the most prevalent valvular heart disease and the 3rd most prevalent cardiovascular disease, after hypertension and coronary artery disease.<sup>1</sup> The prevalence of AS increases with age, from 2% of adults older than 65 years to 4% of adults older than 85.<sup>2</sup> As the average lifespan increases, the burden of senile AS is expected to increase. Aortic stenosis is a progressive condition in which patients are often asymptomatic for years.<sup>3</sup> The duration of the asymptomatic phase can vary widely among individuals. After the onset of symptomatic heart failure, only 50% will survive longer than 2 years without valve replacement.<sup>4</sup> Although sudden cardiac death is a frequent cause of death in symptomatic patients, it appears to be rare ( $<1\%$  per year) in asymptomatic patients.<sup>5-7</sup> Close monitoring and aortic valve replacement surgery (when patients become symptomatic) remain the standard of care.<sup>8,9</sup>

Current American and European guidelines define severe AS as an aortic valve area (AVA) of  $<1$  cm<sup>2</sup> or, indexed by body surface area,  $<0.6$  cm<sup>2</sup>/m<sup>2</sup>.<sup>8,10</sup> The corresponding values are a peak aortic valve velocity of 4 m/s and a mean aortic valve pressure gradient (MG) of  $\geq 40$  mmHg in the presence of normal cardiac output—that is, normal left ventricular ejection fraction (LVEF). Moderate stenosis is characterized by an AVA of 1 to 1.5 cm<sup>2</sup> and an MG of 25 to 40 mmHg. However, not all patients fall into these specific categories of moderate or severe AS as determined by both AVA and MG. Approximately one third of patients sent for echocardiographic evaluation of the severity of AS show a discrepancy in echocardiographic measurements: severe stenosis on the basis of AVA, but non-severe stenosis on the basis of MG, in the presence of a normal LVEF.<sup>11,12</sup> These discrepancies were at first attributed to inaccuracies in echocardiographic measurements and to interobserver variability.

In the past few years, increasing data have suggested that patients with normal LVEF in the presence of severe AS as defined by valve area (AVA,  $<1$  cm<sup>2</sup>) and low valve gradient (MG,  $<40$  mmHg) form a true subgroup. These results appear not to be an anomaly arising from the misreading of echocardiographic measure-

ments.<sup>13-17</sup> This group, known as Low-Gradient Severe AS with preserved LVEF (LGAS), can differ from Low-Flow, Low-Gradient Severe AS patients (AVA <1 cm<sup>2</sup>, MG <40 mmHg, and reduced LVEF ≤0.50), who are known to have a poor prognosis.<sup>18,19</sup> In this latter group, the low gradient is attributed to low cardiac output caused by systolic dysfunction.

Several retrospective studies<sup>20</sup> have suggested that the low gradient in LGAS patients might also be due to reduced stroke volume despite preserved LVEF. Therefore, patients with the LGAS constellation might represent a distinct subgroup with advanced aortic valve disease and impaired ventricular function whose poor prognosis calls for early valve surgery.<sup>20-23</sup> Alternatively, a study published in 2011<sup>24</sup> showed LGAS patients to have clinical outcomes similar to those of patients with moderate AS. Because of the present lack of clarity on how the LGAS group progresses and on where it fits within the continuum of AS severity, we examined an unselected population diagnosed with AS and chose to study the prevalence and progression of LGAS—as well as the natural progression of various other categories of AS into LGAS.

## Patients and Methods

In this retrospective study, we included patients who had undergone 2 transthoracic echocardiograms at the University of Pittsburgh Medical Center. The first of these studies had to show an AVA ranging from 0.6 to 2 cm<sup>2</sup> and had to have been performed from the end of November 2004 through the end of November 2005; the 2nd had to have been performed from the end of November 2006 through the end of November 2007. Patients were excluded if they had >2+ aortic regurgitation, rheumatic valve disease, a bicuspid aortic valve, a prosthetic aortic valve, other moderate-to-severe valvular heart disease, an LVEF ≤0.50, hypertrophic cardiomyopathy, or a transplanted heart. Demographic, clinical, and laboratory data were obtained by reviewing medical records. Patients' echocardiograms (in the health system's electronic database) were chosen for screening whenever AS was mentioned in the referral diagnosis, in the body of the echocardiogram report, or in the final diagnosis. An initial 4,270 patients were screened for inclusion in the study; 4,154 of these were excluded because they did not meet our specified criteria.

### Clinical and Laboratory Data

Clinical data included information on age, sex, coronary artery disease (history of myocardial infarction, angioplasty, coronary artery bypass grafting, or coronary artery disease as determined by angiography [epicardial coronary stenosis, >50%]), hypertension, current smoking, diabetes mellitus, and end-stage renal disease.

### Transthoracic Echocardiography

All echocardiographic data had been obtained by an experienced sonographer, interpreted by an experienced staff echocardiographer, and entered into the institutional electronic record. Staff echocardiographers were blinded to the conduction of the present study. The AVA was calculated by means of the continuity equation.<sup>25-27</sup> Patients with >2+ aortic regurgitation were excluded to avoid a confounding increase in forward-flow hemodynamic data.<sup>28,29</sup> Patients' severity of AS was classified on the basis of AVA: mild AS (AVA, ≥1.5 cm<sup>2</sup>), moderate AS (AVA, 1 to <1.5 cm<sup>2</sup>), and severe AS (AVA, <1 cm<sup>2</sup>). Severe AS was further classified as LGAS or high-gradient severe AS (HGAS) on the basis of MG. Low-gradient AS was defined as an MG of <40 mmHg; LGAS patients therefore had an AVA of <1 cm<sup>2</sup>, an MG of <40 mmHg, and an LVEF of >0.50. High-gradient AS was defined as an MG of ≥40 mmHg; HGAS patients therefore had an AVA of <1 cm<sup>2</sup> and an MG of ≥40 mmHg. Patients who had LGAS were compared with the remaining (uncategorized) patients in the AS study group, who had been called simply the "non-LGAS" group. The median time interval between initial and follow-up echocardiograms was 698 days (range, 371–1,020 d).

### Statistical Analysis

Baseline characteristics of the LGAS and non-LGAS groups were compared by means of the Pearson  $\chi^2$  test for discrete variables and the Student *t* test for continuous variables. The one-way analysis of variance procedure was used to test hypotheses if several means were equal. The Tukey test was used for post hoc comparisons between pairs of means. For both AVA and MG, the progression of AS was measured in terms of annual change (that is, initial value – follow-up value × 365 follow-up days). Multiple linear regression was used to predict AVA and MG changes from baseline levels and follow-up time. Kaplan-Meier analysis with the log rank test was used to examine the temporal trend of LGAS (versus moderate AS) to become severe HGAS during follow-up. A *P* value cutoff of <0.05 was used to signify statistical significance. Statistical analysis was performed with use of SPSS 17.0 (IBM Corporation; Armonk, NY).

## Results

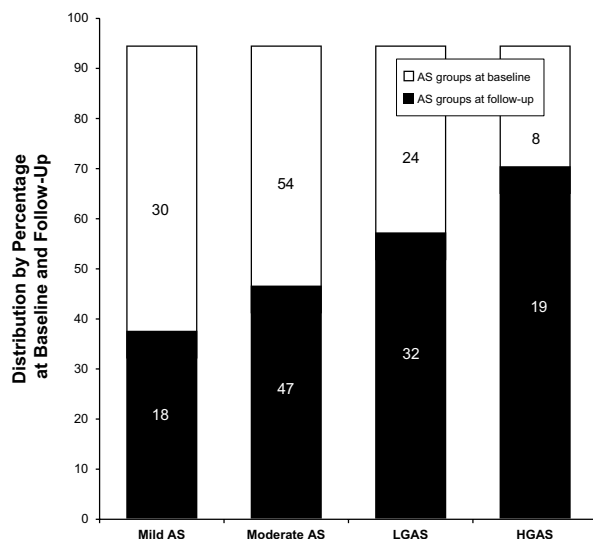
Upon baseline echocardiographic testing of the 116 patients who met the criteria for the study, 24 (21%) were in the LGAS group and the remaining 92 (79%) were in the non-LGAS group (mild AS, 30 [26%]; moderate AS, 54 [47%]; and HGAS, 8 [7%]). At follow-up, the distribution was mild AS (18 patients, or 16%), moderate AS (47 patients, or 40%), LGAS (32 patients, or 28%), and HGAS (19 patients, or 16%), which differed

significantly from baseline (Pearson  $\chi^2$ , 74.1;  $P < 0.001$ ). The LGAS group had a higher prevalence of myocardial infarction and coronary artery disease than did the HGAS group ( $P < 0.05$ ) but did not differ significantly from the moderate group in those regards.

### Progression of Aortic Stenosis

Figure 1 shows the distribution of patients in the 4 groups at the baseline and follow-up echocardiograms. Table I shows the baseline and follow-up echocardiographic values of the LGAS group in comparison with those of the non-LGAS groups. The annual change of AVA and MG for the entire cohort was  $-0.09 \pm 0.14 \text{ cm}^2$  (decrease in AVA) and  $2 \pm 6 \text{ mmHg}$  (increase in MG). The univariate predictors of annual change in AVA are male sex ( $P < 0.013$ ) and small baseline AVA ( $P < 0.001$ ). The multivariate predictor of annual change in AVA is baseline AVA ( $P < 0.001$ ). The only significant univariate predictor of annual change in MG was baseline MG ( $P = 0.017$ ). The regression equation for annual AVA change is  $-0.17 \times \text{AVA} (\text{cm}^2) - 0.12$  ( $r = 0.4$ ,  $P < 0.001$ ); for annual MG change, the regression equation is  $0.11 \times \text{MG} (\text{mmHg}) - 4.8$  ( $r = 0.23$ ,  $P = 0.02$ ).

Annual decreases in AVA were  $-0.16 \pm 0.15 \text{ cm}^2$  for mild AS,  $-0.08 \pm 0.15 \text{ cm}^2$  for moderate AS,  $-0.03 \pm 0.07 \text{ cm}^2$  for LGAS, and  $-0.03 \pm 0.05 \text{ cm}^2$  for HGAS ( $P = 0.004$  between groups;  $P < 0.002$  for LGAS vs mild AS;  $P = 0.264$  for LGAS vs moderate AS; and  $P = 1.0$  for LGAS vs HGAS).



**Fig. 1** Distribution (by absolute numbers and by percentages) of 116 aortic stenosis patients by group at initial echocardiogram (white segments) and at follow-up (black segments). The numbers inside each colored segment are the absolute numbers of patients in that group at that time. Note the trend toward increasing proportions of low- and high-gradient aortic stenosis cases over time.

AS = aortic stenosis; HGAS = high-gradient aortic stenosis; LGAS = low-gradient aortic stenosis

Annual increases in MG were  $1 \pm 3 \text{ mmHg}$  for mild AS,  $1.8 \pm 5 \text{ mmHg}$  for moderate AS,  $4.8 \pm 9 \text{ mmHg}$  for LGAS, and  $1.5 \pm 7 \text{ mmHg}$  for HGAS ( $P = 0.052$  between groups;  $P = 0.09$  between LGAS vs HGAS).

### Comparison of Low-Gradient Aortic Stenosis with Moderate Aortic Stenosis

Median follow-up intervals for the moderate and LGAS groups were similar (683 vs 716 d;  $P = 0.25$ ). During follow-up, 6 patients in the LGAS group (25%) had increased MG  $> 40 \text{ mmHg}$  and became HGAS. In the moderate-AS group, 13 (24%) progressed to LGAS and 7 (13%) progressed to HGAS. Kaplan-Meier analysis showed the distribution of time in which LGAS and moderate-AS patients reached HGAS status (Fig. 2). Because less than 50% of patients reached HGAS status in one of the groups, median survival time was not calculated. However, we did compare the 2 groups' first-quartile (25%) survival curves. For the moderate-AS group, the progression rate to HGAS (at follow-up) was longer than for the LGAS group (881 vs 713 d; difference, 161 d;  $P = 0.035$ ).

In terms of annual change in AVA, there was no statistically significant difference between the LGAS group and the moderate-AS group ( $-0.03 \pm 0.07$  vs  $-0.08 \pm 0.15 \text{ cm}^2$ ;  $P = 1.0$ ). However, in terms of annual change in MG, the LGAS group tended to have a higher rate of progression ( $4.8 \pm 9$  vs  $1.8 \pm 5 \text{ mmHg}$ ;  $P = 0.09$ ).

## Discussion

Previous studies have indicated that the average rate of progression of calcific AS is a reduction in valve area of about  $0.1 \text{ cm}^2$  per year and an average increase in MG of  $7 \text{ mmHg}$ .<sup>5,30,31</sup> Our total study group (LGAS together with non-LGAS) showed an annual reduction in AVA of  $0.09 \pm 0.14 \text{ cm}^2$ , a rate similar to those of previous studies. Considered separately, the annual AVA reduction rates were  $0.03 \pm 0.07 \text{ cm}^2$  for the LGAS group and  $0.1 \pm 0.15 \text{ cm}^2$  for the non-LGAS group).

### Low- and High-Gradient Aortic Stenosis at Baseline

Low-gradient AS is observed in a significant proportion of AS patients (21% in our sample). Whether this finding arises from echocardiographic discrepancies in AVA and MG or from the presence of a distinct subgroup of patients has been controversial. When we compared LGAS with HGAS with respect to annual rate of change in AVA, there was no significant difference ( $0.03 \pm 0.07$  vs  $0.03 \pm 0.05 \text{ cm}^2$ ;  $P = 1.0$ ). However, in terms of annual change in MG, LGAS tended to display a higher rate of change than did HGAS, without reaching statistical significance ( $4.8 \pm 9$  vs  $1.5 \pm 7 \text{ mmHg}$ ;  $P = 0.09$ ). This is not surprising, because these groups at baseline had similar AVA (approximately  $0.8 \text{ cm}^2$ ), but signifi-

**TABLE I.** Baseline and Follow-Up Echocardiographic Variables in the Low-Gradient Aortic Stenosis and the Mild, Moderate, and High-Gradient Aortic Stenosis Groups

Variable	Low-Gradient AS n=24 (21)	Mild AS n=30 (26)	P Value <sup>a</sup>	Moderate AS n=54 (47)	P Value <sup>b</sup>	High-Gradient AS n=8 (6)	P Value <sup>c</sup>
Age (yr)	81 ± 8	74 ± 11	NS	75 ± 12	NS	72 ± 10	NS
Male sex	12 (50)	21 (70)	NS	32 (59)	NS	3 (38)	NS
<b>Baseline</b>							
AVA (cm <sup>2</sup> )	0.83 ± 0.08*	1.7 ± 0.13***	<0.001	1.2 ± 0.14***	<0.001	0.8 ± 0.12	NS
Peak gradient (mmHg)	46 ± 11*	26 ± 8.6	<0.001	35 ± 13***	<0.01	77 ± 14	<0.001
Mean gradient (mmHg)	28 ± 6**	15 ± 5.6	<0.001	23 ± 12**	NS	53 ± 5	<0.001
LVEF	0.59 ± 0.06	0.59 ± 0.06	NS	0.60 ± 0.06	NS	0.59 ± 0.06	NS
<b>Follow-Up</b>							
AVA (cm <sup>2</sup> )	0.76 ± 0.13	1.4 ± 0.28	<0.001	1.0 ± 0.27	<0.001	0.73 ± 0.16	<0.01
Peak gradient (mmHg)	55 ± 19	28 ± 9.5	<0.001	44 ± 21	0.05	82 ± 18	<0.01
Mean gradient (mmHg)	36 ± 16	17 ± 6.4	<0.001	27 ± 13	<0.01	51 ± 9	0.02
LVEF	0.57 ± 0.09	0.60 ± 0.08	NS	0.59 ± 0.06	NS	0.61 ± 0.06	NS

AS = aortic stenosis; AVA = aortic valve area; LVEF = left ventricular ejection fraction; NS = not significant

<sup>a</sup> Pooled comparison between low-gradient AS versus mild-AS group,

<sup>b</sup> Pooled comparison between low-gradient AS versus moderate-AS group,

<sup>c</sup> Pooled comparison between low-gradient AS versus high-gradient-AS group.

Pairwise comparison between baseline and follow-up: \**P* < 0.05; \*\**P* < 0.01; \*\*\**P* < 0.001

Values are stated as mean ± SD or as number and percentage. *P* < 0.05 was considered statistically significant.

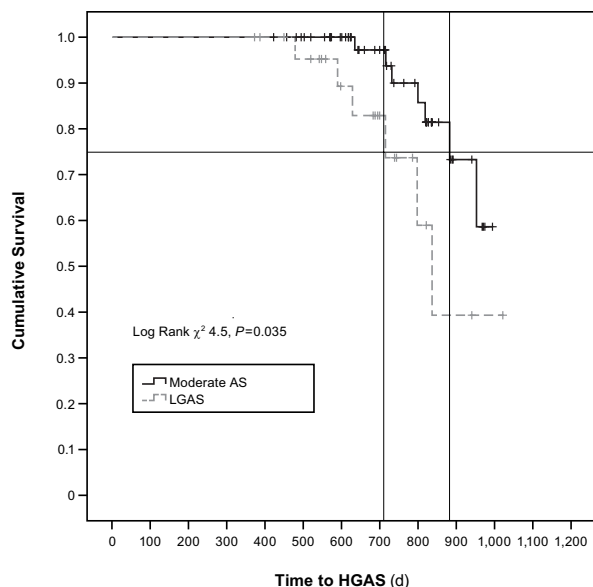
cantly different MG (LGAS, 28 mmHg vs HGAS, 53 mmHg; *P* < 0.001). From the perspective of progression to HGAS, LGAS patients appear to be more advanced than moderate-AS patients. At the same time, LGAS patients (having similar AVA but lower MG) are not more advanced than HGAS patients. Therefore, LGAS probably represents an intermediate stage between moderate AS and HGAS. Another important finding in our study is that patients with moderate AS generally progress to LGAS and then to severe AS. This is in contrast with the suggestions of other retrospective studies<sup>20-23</sup> that patients with LGAS might represent a subgroup of patients with an advanced stage of severe AS, characterized by reduced stroke volume due to impaired ventricular function, despite preserved LVEF. Our study was not designed to evaluate the symptomatic status and progression of AS. However, valvular AS is indeed progressive and life threatening. Once symptoms appear, untreated patients have a poor prognosis; they will experience worsening symptoms, eventually leading to death. After the onset of symptoms, the average survival rate is 50% at 2 years and 20% at 5 years.<sup>32</sup> However, we observed no death in any of our AS groups over the median interval of 698 days (range, 371–1,020 d).

### Low-Gradient and Moderate AS

At baseline, the LGAS group had significantly lower AVA and tended to have higher MG than did the moderate-AS group. In its annual progression of AVA, the LGAS group tended to progress at a lower (but statistically insignificant) rate than did the moderate-AS group (0.03 vs 0.08 cm<sup>2</sup>; *P* = 0.26). This can be explained by the lower AVA of LGAS: AVA is a predictor of annual area decline. However, the LGAS group tended to have a higher rate of MG increase than did the moderate-AS group (4.8 vs 1.8 mmHg; *P* = 0.23). This can be explained by the higher baseline MG of the LGAS group: baseline MG is a predictor of annual increase of MG. In regard to the progression to HGAS during follow-up, LGAS reached the HGAS stage more rapidly than did the moderate-AS group, as evidenced by differences in the actuarial curves.

### Progression of Low-Gradient Aortic Stenosis

The progression of aortic disease in the LGAS group was slower by AVA but higher by MG than in the non-LGAS group (−0.03 ± 0.07 vs −0.10 ± 0.15 cm<sup>2</sup> and 4.8 ± 9 vs 1.28 ± 4.9 mmHg, respectively; *P* < 0.03 and *P* < 0.02, respectively). The regression equation to predict



**Fig. 2** Kaplan-Meier curve for progression of low-gradient aortic stenosis (LGAS) and moderate aortic stenosis (AS) to high-gradient aortic stenosis (HGAS). The vertical axis shows the probability of survival (that is, of not progressing to HGAS). In this plot, drops in the survival curve occur whenever the patient reaches HGAS status at follow-up. The thin horizontal line passes through 0.75 and cuts through points on both curves. At that point, the curve shows the probability that a patient will not have reached HGAS status by that time. In this study, by 713 days 75% of patients in the LGAS group had not reached HGAS, whereas by 881 days 75% of patients in the moderate-AS group had not reached HGAS. In other words, 25% (first quartile) of patients in LGAS reached HGAS status significantly earlier than 25% (first quartile) of patients in the moderate-AS group (713 vs 881 d;  $P=0.035$ ).

AVA or MG for the LGAS group (mentioned above) did not yield a statistically significant result, but for the entire AS group it was significant. For the entire AS group, AVA was reduced by  $0.17 \text{ cm}^2$  per year at follow-up, and MB was increased by  $5 \text{ mmHg}$  per year.

### Probable Mechanism of LGAS

Several mechanisms might account for a low-pressure gradient in combination with a markedly reduced AVA in the presence of a preserved LVEF.

First, it is possible that the values of AVA and gradient measurement by which we label the severity of AS (in accordance with guidelines) are arbitrary and inconsistent with the true severity of the disease. A valve area of  $1 \text{ cm}^2$  might not always correlate with an MG of  $40 \text{ mmHg}$  or with an aortic velocity of  $4 \text{ m/s}$ .

Second, echocardiographic measurements of valve area and gradient have always been plagued with inter- and intraobserver variability and with the difficulties that accompany actual Doppler measurement. Echocardiography tends to underestimate the left ventricular outflow tract (LVOT) diameter, partly because of the tract's elliptical rather than circular anatomy.<sup>25,33</sup> Small

errors in the measurement of LVOT diameter will result in substantial errors in calculating AVA, since the square of the radius is used in the continuity equation. Because this subgroup of patients has normal LVEF, it is presumed that these patients have normal cardiac output. Although diastolic filling abnormalities can result in decreased stroke volume, prior studies that have used catheter-based calculations have shown LGAS in the presence of normal stroke volume.<sup>12,24,34</sup>

Third, although it is possible that the presence of systemic hypertension or increased arterial stiffness might result in lower-than-expected gradients obtained by Doppler measurement,<sup>35</sup> the consistent presence of LGAS in cross-studies of different groups increases the likelihood that LGAS is a distinct entity.

### Study Limitations

This was a nonrandomized, retrospective, and observational study. Therefore, it generates only hypotheses and requires external confirmation, ultimately by a prospective trial. It was not possible to adjust for all potential confounders, known or unknown, that could have affected the detected difference. Our exclusion of patients with greater-than-moderate aortic regurgitation, depressed ventricular function, or fewer than 2 echocardiograms prevents our generalizing the findings by applying them to patients with such characteristics. This observational analysis is subject to selection bias. The retrospective nature of the study prevented our matching baseline LVOT diameters with follow-up LVOT diameters—hence AVA measurement might have been affected. Because symptoms were not included in the study, our study findings in regard to natural disease progression and the advisability of more frequent echocardiographic examinations in these patients might be difficult to implement in a clinical setting without further trials that examine symptomatology.

### Summary

In contrast to previous studies that suggest that LGAS is either a moderate-AS or severe-AS group, we suggest that LGAS is a unique subgroup lying between the two. Perhaps all AS patients should be classified into 4 groups as mild, moderate, LGAS, or HGAS, instead of the 3 groups now in use. Because LGAS patients have not reached the severest form of AS (HGAS), they can be monitored safely with serial clinical and echocardiographic evaluation. In contrast, because the disease is worse than in the moderate-AS group, follow-up evaluations should be more frequent than in the moderate-AS group, probably every 3 to 6 months.

This study is valuable, first, insofar as readers should know that the LGAS condition is not uncommon in an unselected population with AS. Second, the study supports the perception that, in terms of progression, LGAS

lies between moderate AS and severe AS (HGAS). Third, echocardiographic studies can be an important part of an integrated approach to the asymptomatic patient. The American College of Cardiology/American Heart Association task force (1998) recommends an echocardiogram for severe AS every year, and for moderate stenosis every 2 years. On the basis of LGAS's significantly rapid progression to HGAS (in comparison with the progression of moderate AS to HGAS), more frequent monitoring is reasonable. It might be possible to safely withhold surgery in this group of patients (who are asymptomatic) and to choose "watchful waiting" as a viable option. Further research with randomized clinical trials is needed before we can decide on the best treatment option for this subgroup. Both diastolic filling abnormalities and cardiac output in LGAS patients merit further study.

### Conclusion

Because LGAS is relatively common in patients with aortic stenosis and has a high propensity to progress to HGAS, we propose that LGAS patients be closely monitored as a subgroup of AS patients who are unique and warrant more frequent echocardiographic follow-up than do patients with moderate AS.

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