Aortic valve disease: multimodality imaging for risk stratification and evaluation of therapy

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ASSOCIATION OF LEFT VENTRICULAR GLOBAL LONGITUDINAL STRAIN WITH ASYMPTOMATIC SEVERE AORTIC STENOSIS: NATURAL COURSE AND PROGNOSTIC VALUE

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ABSTRACT

IMPORTANCE

The optimal timing to operate in patients with asymptomatic severe aortic stenosis (AS) remains controversial. Left ventricular global longitudinal strain (LV GLS) may help to identify patients who might benefit from undergoing earlier aortic valve replacement.

OBJECTIVE

To investigate the prevalence of impaired LV GLS, the natural course of LV GLS, and its prognostic implications in patients with asymptomatic severe AS with preserved left ventricular ejection fraction (LVEF).

DESIGN, SETTING, AND PARTICIPANTS

This registry-based study included the institutional registries of 3 large tertiary referral centers and 220 patients with asymptomatic severe AS and preserved LVEF (>50%) who were matched for age and sex with 220 controls without structural heart disease. The echocardiograms of patients and controls were performed between 1998 and 2017.

EXPOSURES

Both clinical and echocardiographic data were assessed retrospectively. Severe AS was defined by an indexed aortic valve area <0.6 cm^2/m^2. Left ventricular global longitudinal strain was evaluated on transthoracic echocardiography using speckle tracking imaging.

MAIN OUTCOMES AND MEASURES

The prevalence of impaired LV GLS, the natural course of LV GLS, and the association of impaired LV GLS with symptom onset and the need for aortic valve intervention.

RESULTS

Two-hundred twenty patients (mean age 68±13 years; 126 men [57%]) were included. Despite comparable LVEF, LV GLS was significantly impaired in patients with asymptomatic severe AS compared with age- and sex-matched controls without AS (mean LV GLS, -17.9±2.5% vs. -19.6±2.1%; P<0.001). After a median follow-up of 12 (interquartile range [IQR]: 7 to 23) months, mean LV GLS significantly deteriorated (-18.0±2.6% to -16.3±2.8%; P<0.001) while LVEF remained unchanged. Patients with impaired LV GLS at baseline (>-18.2%) showed a higher risk for developing symptoms (P=0.02) and needing aortic valve intervention (P=0.03) at follow-up compared with patients with more preserved LV GLS (≤-18.2%).

CONCLUSIONS AND RELEVANCE

Subclinical myocardial dysfunction that is characterized by impaired LV GLS is often present in patients with asymptomatic severe AS with preserved LVEF. Left ventricular global longitudinal strain further deteriorates over time and impaired LV GLS at baseline is associated with an increased risk for progression to the symptomatic stage and the need for aortic valve intervention.

Introduction

In patients with asymptomatic severe aortic stenosis (AS), the current guidelines recommend a watchful waiting strategy until symptoms or left ventricular (LV) systolic dysfunction (i.e., LV ejection fraction [LVEF] <50%) develop [1, 2]. The optimal timing for intervention in these patients remains controversial [3–6]. To determine whether the patients are truly asymptomatic, exercise testing is animportant diagnostic tool [7]. However, in patients who are unable to perform this test, additional measurements are needed to better define the timing of the intervention. The assessment of LV systolic function by means of global longitudinal strain (GLS) by speckle tracking echocardiography has demonstrated that a significant proportion of patients with severe AS have impaired LV GLS despite having normal LVEF [8–13]. Impaired LV GLS has been associated with worse outcomes in patients with symptomatic severe AS [14]. However, to our knowledge, the prevalence of impaired LV GLS among patients with asymptomatic severe AS and normal LVEF and the natural course and prognostic value of LVGLS in this subgroup of patients has not been extensively elucidated. Accordingly, this study aimed to investigate the prevalence of impaired LV GLS, as well as describing the natural course of serial changes in LV GLS and its prognostic implications, in asymptomatic patients with severe AS and preserved LVEF.

Methods

Study population and data collection

From a multicenter international registry of patients with AS (Leiden University Medical Center [Leiden, The Netherlands], HeartValve Clinic [Liège, Belgium], and Institut Universitaire de Cardiologie et de Pneumologie de Québec [Quebec, Canada]), 220 patients with asymptomatic severe AS and preserved LV ejection fraction (LVEF >50%) were selected and included in this retrospective study. Patients were selected based on available echocardiographic data at baseline (defined as the date of the first diagnosis of severe AS) with a feasible speckle tracking analysis. The definition of severe AS was based on an indexed aortic valve area (AVA) <0.6 cm^2/m^2 and/or a mean aortic valve gradient of ≥40 mmHg and/or a peak aortic jet velocity ≥4 m/s [2, 15, 16]. When available, the last transthoracic echocardiogram performed at the outpatient clinic or before aortic intervention was analyzed to evaluate the changes in valve hemodynamics, LV structure, and systolic function (including LV GLS). Measurements of the echocardiographic data were performed at each institution by experienced observers. Aortic valve intervention was defined as a surgical or transcatheter aortic valve replacement (AVR) or balloon valvuloplasty. The exclusion criteria were AS-related symptoms at baseline (e.g., angina, syncope, or dyspnea), nonsevere AS, LVEF <50%, having undergone prior aortic or mitral valve intervention, acute endocarditis at baseline, or the inability to measure LV GLS.

In addition, an age- and sex-matched control group of 220 individuals without structural heart disease was included and used as a reference for measuring LV GLS. The transthoracic echocardiograms of this group of individuals were performed at the Leiden University Medical Center. The referral reasons to perform echocardiography in this group were atypical chest pain, palpitations, or syncope without the presence of a murmur.

Baseline patient demographics and clinical follow-up data were gathered and analyzed retrospectively using the departmental patient information systems and hospital records. This retrospective analysis of clinically acquired data was approved by the respective institutional review boards of each participating center, and consent was waived due to the retrospective nature of the study.

TRANSTHORACIC ECHOCARDIOGRAPHY

Transthoracic echocardiography was performed in all patients at rest in the left decubitus position using commercially available ultrasonography systems. Conventional LV dimensions and function as well as AVA were measured following current recommendations [17]. Additionally, LV GLS was measured with a 2-dimensional speckle tracking analysis on apical 2-, 3-, and 4-chamber views using commercially available software (Leiden University Medical Center: EchoPac, version 113; General Electric; Vingmed Ultrasound; Heart Valve Clinic Liège and Institut Universitaire de Cardiologie et de Pneumologie de Québec: 2D Cardiac Performance Analysis; TomTec Imaging Systems) [17]. The frame rate of the 2-dimensional echocardiographic data was ≥40 frames per second. Left ventricular GLS measures the shortening of the myocardial fibers in the longitudinal direction and is conventionally presented as a negative value. Therefore, a less negative LV GLS (i.e., closer to 0) represents worse LV systolic function.

CLINICAL AND ECHOCARDIOGRAPHIC FOLLOW-UP AND ENDPOINTS

Patients were routinely followed up at the outpatient clinic according to guideline recommendations [16]. The onset of AS-related symptoms was recorded. The medical treatment and timing for AVR was left at the discretion of the treating physician of each institution. The time to symptom development and AVR, as well as the date of all-cause mortality, were recorded as clinical end points for assessing the prognosis.

STATISTICAL ANALYSIS

Categorical variables were presented as numbers (percentage) and continuous variables as mean±SD if normally distributed or medians (interquartile range [IQR]) if otherwise. Histograms were used to evaluate if a Gaussian distribution was present. Comparisons between the total asymptomatic severe AS group and the control group were performed using the *t* test or Mann-Whitney *U* test for continuous variables and the χ^2 test or Fisher exact test for categorical variables as appropriate. The group of patients with asymptomatic severe AS was divided according to the symptom status at the last echocardiogram performed: symptomatic vs. asymptomatic. Changes within and between these 2 groups were assessed using linear mixed models, with correction for age, sex, and time to follow-up. To further examine the prognostic value of LV GLS, the study population was divided according to the median baseline LV GLS value. Cumulative event rates were calculated with the Kaplan-Meier method. Two end points were defined: new onset of symptoms and AVR. Comparisons between the 2 groups were performed using log-rank tests. To assess the association between baseline LV GLS and the end points, Cox proportional hazards modeling was used. Spline models were fitted with overlaying confidence intervals for each end point vs. LV GLS on the log-hazards scale, adjusting for age, sex, coronary artery disease, atrial fibrillation, and LV mass index. SPSS, version 23.0 (IBM,

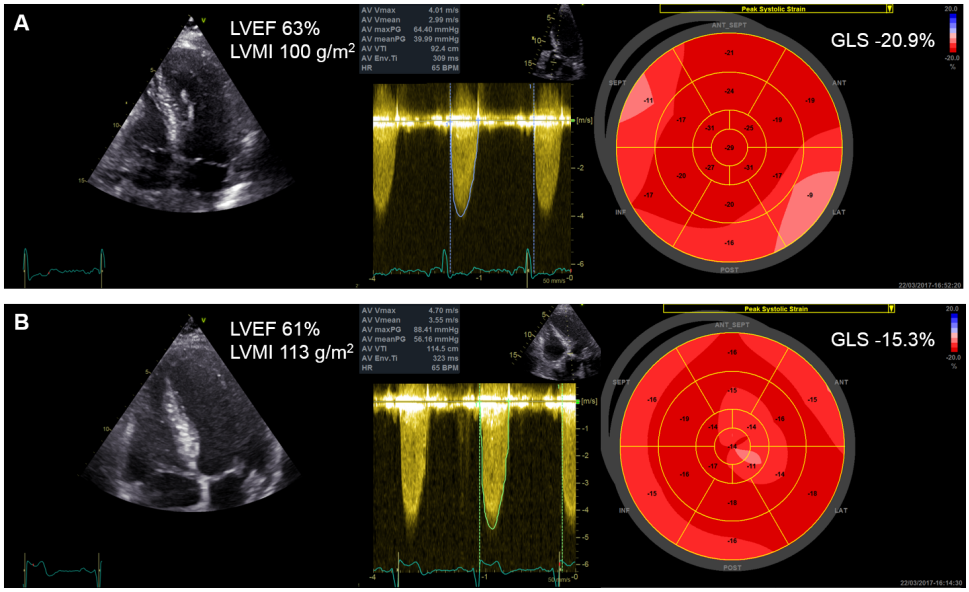

Figure 1: Example of a patient with asymptomatic severe aortic stenosis and preserved left ventricular (LV) ejection fraction (LVEF) at baseline (*panel A*) and at follow-up (*panel B*). Over time, the aortic stenosis severity and LV hypertrophy progressed and LV systolic function as assessed with LV global longitudinal strain (GLS) deteriorated, whereas LVEF remained unchanged. LVMI, left ventricular mass index.

Armonk, New York) was used for the statistical analyses. A *P* value of <0.05 was considered statistically significant.

Results

Characteristics of patients with asymptomatic severe AS vs. controls

In total, 220 patients with asymptomatic severe AS and preserved LVEF (mean age 68±13 years; 126 men [57%]) were evaluated in this study (Table 1). Despite comparable LVEF, LV GLS was significantly impaired in the patients with asymptomatic severe AS compared with controls, suggesting that asymptomatic patients with severe AS can harbor subtle myocardial dysfunction. When using the mean LV GLS value of the control group as a reference to define normal (≤-19.6%) or impaired LV longitudinal systolic function (>-19.6%), 153 patients (70%) with asymptomatic severe AS had impaired LV GLS. Left ventricular global longitudinal strain was not significantly different across the centers (Leiden, -18.2±2.3%; Québec, -18.0±1.8%; Liège, -17.4±3.1%]; analysis of variance *P*=0.15). In addition, there were no differences across the centers in the proportion of patients with impaired LV GLS (Leiden, 65%; Québec, 81%; Liège, 73%; *P*=0.20).

Table 1: Baseline clinical and echocardiographic characteristics of asymptomatic severe aortic stenosis patients and an age- and sex-matched cohort of individuals without structural heart disease.

Variables	Patients with asymptomatic severe AS (N = 220)	Age- and sex-matched cohort (N = 220)	*P* value
Clinical characteristics			
Age, years	67.9±13.0	65.7±13.3	0.08
Male gender, *N* (%)	126 (57)	126 (57)	1.00
Body surface area, m^2	1.87±0.2	1.93±0.2	**0.002**
Hypertension, *N* (%)	128 (59)	103(48)	**0.02**
Hypercholesterolemia, *N* (%)	103 (47)	54 (25)	**<0.001**
Diabetes, *N* (%)	34 (16)	24 (11)	0.16
History of smoking, *N* (%)	73 (38)	17 (11)	**<0.001**
Coronary artery disease, *N* (%)	47 (22)	0 (0)	**<0.001**
Prior myocardial infarction, *N* (%)	15 (7)	0 (0)	**<0.001**
Medication use, *N* (%)			
Beta-blocker	78 (36)	49 (23)	**0.002**
ACE-inhibitor/ARB	88 (40)	65 (30)	**0.02**
Calcium antagonist	48 (22)	23 (11)	**0.001**
Diuretic agents	52 (24)	44 (20)	0.34
Statins	112 (51)	56 (26)	**<0.001**
Aspirin and/or clopidogrel	93 (43)	48 (22)	**<0.001**
Vitamin K antagonist or NOAC	31 (14)	3 (1)	**<0.001**
Creatinin level, µmol/l	80 [70-97]	80 [69-93]	0.56
Estimated GFR, ml/min/1.73 m^2	76 [61-89]	80 [65-89]	0.48
Baseline echocardiography			
Valve anatomy, *N* (%)			**<0.001**
Tricuspid	170 (77)	220 (100)	
Bicuspid	50 (23)	0 (0)	
Aortic valve mean gradient (mmHg)*	39.4±12.6	N/A	N/A
Aortic valve peak velocity (m/s)*	4.0±0.6	N/A	N/A
Aortic valve area (cm^2)*	0.86±0.1	N/A	N/A
Aortic valve area index (cm^2/m^2)*	0.46±0.1	N/A	N/A
Stroke volume (ml)*	81.4±17.1	N/A	N/A
Stroke volume index (ml/m^2)*	43.8±9.1	N/A	N/A
LV end-diastolic diameter (mm)	45.4±5.8	48.5±6.4	**<0.001**
LV end-systolic diameter (mm)	28.2±5.0	30.5±6.5	**<0.001**
Intraventricular septal thickness (mm)	12.9±2.3	10.3±1.7	**<0.001**
Posterior wall thickness (mm)	11.6±1.9	10.0±2.0	**<0.001**
LV mass index (g/m^2)	112.0±27.7	92.5±21.4	**<0.001**
LV ejection fraction (%)	61.5±5.9	62.1±6.3	0.27
LV global longitudinal strain (%)	-17.9±2.5	-19.6±2.1	**<0.001**

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; AS, aortic stenosis; GFR, glomerular filtration rate estimated using CKD-EPI formula; LV, left ventricular; N/A, not applicable; NOAC, novel oral anti-coagulants. *Aortic valve gradients, aortic valve area, and stroke volume were only measured for patients with AS.

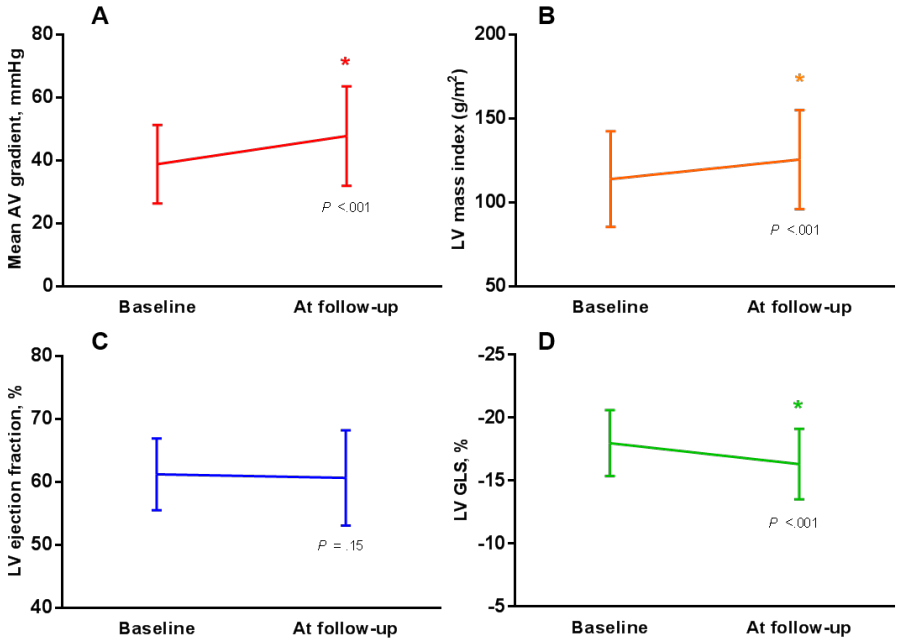

Figure 2: Time course of valve hemodynamics and left ventricular systolic function in 150 patients with asymptomatic severe aortic stenosis at baseline vs. follow-up echocardiography by aortic valve (AV) mean gradient (*panel A*), left ventricular (LV) hypertrophy (*panel B*) and LV systolic function by LV ejection fraction (*panel C*) and LV global longitudinal strain (GLS)(*panel D*). *Indicates *P*<0.001.

Changes in LV GLS over time in patients with AS

To evaluate the changes in LV GLS in patients with asymptomatic severe AS, a subgroup of 150 patients (68.2%) with severe AS with an available second transthoracic echocardiogram result (at the last clinical follow-up or before AVR) and a feasible speckle tracking analysis result was evaluated. The median time interval between the 2 echocardiograms was 12 (IQR: 7 to 23) months. The changes in valve hemodynamics and LV systolic function are displayed in Supplemental Table 3. Over time, there were significant increases in mean transvalvular gradients and LV mass index, whereas the AVA decreased. While the LVEF remained unchanged (61.2±5.7% to 60.6±7.6%; *P*=0.15), LV GLS showed significant impairment over time (-18.0±2.6% to -16.3±2.8%; *P*<0.001) (Figures 1 and 2), demonstrating increasing subclinical LV dysfunction over time.

Of the 150 patients with echocardiographic follow-up and feasible speckle tracking analysis, 78 (52%) were symptomatic at follow-up echocardiography and 72 patients (48%) remained asymptomatic. The median time from baseline to follow-up echocardiography was similar between these 2 groups (symptomatic, 13 [IQR: 8 to 28] months vs. asymptomatic, 12 [IQR: 6 to 20] months; *P*=0.09). Compared with asymptomatic patients, patients who developed symptoms at follow-up showed a higher prevalence of atrial fibrillation (22% vs. 10%, respectively; *P*=0.05) and had more frequent coronary

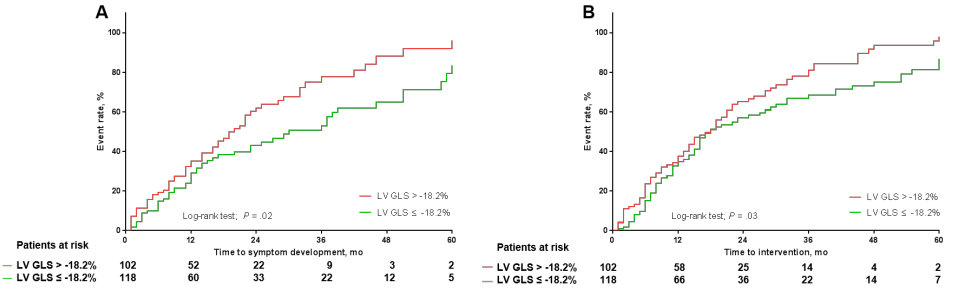

Figure 3: Kaplan-Meier estimates for event rates for symptom development (*panel A*) and intervention (*panel B*) in patients with asymptomatic aortic stenosis. Cumulative event rates were compared with the study population divided according to left ventricular (LV) global longitudinal strain (GLS) at baseline >-18.2% (more impaired, red line) vs. ≤-18.2% (more preserved, green line).

artery disease (27% vs. 16%, respectively; *P*=0.09). Table 2 outlines the changes in valve hemodynamics and LV systolic function over time in these patients divided by symptom status at follow-up. Within both groups, the progression of AS was observed over time with a concomitant increase in LV mass index and impairment in LV GLS without changes in LVEF. Between both groups, no significant differences were observed in valve hemodynamics and LV systolic function, although LV mass index at follow-up was higher in patients with AS who developed symptoms.

PROGNOSTIC VALUE OF LV GLS IN SYMPTOM DEVELOPMENT AND AVR

Of the 220 patients with asymptomatic severe AS, 118 (54%) developed symptoms during a median follow-up of 12 months (IQR, 5-24). After a median follow-up period of 13 (IQR: 6 to 25) months, 162 patients (74%) received an aortic valve intervention (28 [17%] received transcatheter aortic valve implantation, 130 [80%] underwent surgical AVR, and 4 [3%] underwent balloon valvuloplasty). Most of these patients underwent aortic valve intervention because of symptom development (104 [64%]) or progression of AS severity (40 [25%]); only 18 patients (11%) received an AVR because of other reasons, such as an indication for coronary artery bypass grafting. During follow-up, 28 patients (13%) died; 8 patients (4%) died while scheduled for AVR or when receiving conservative treatment.

To evaluate the prognostic value of baseline LV GLS, the study population was divided into 2 groups according to the median value of baseline LV GLS (more preserved, ≤-18.2% vs. more impaired, >-18.2%) Supplemental Table 4). Compared with patients with more preserved LV GLS, patients with more impaired LV GLS had a higher prevalence of coronary artery disease (30% vs. 15%, *P*=0.01) and atrial fibrillation (26% vs. 12%, *P*=0.01). On transthoracic echocardiography, patients with more impaired LV GLS had a larger LV mass index and lower LVEF than patients with more preserved LV GLS, although mean LVEF was >60% in both groups (Supplemental Table 4).

The cumulative event rates for developing symptoms were significantly higher in patients with a baseline LV GLS >-18.2% compared with patients with an LV GLS ≤-18.2% (59% vs. 45% at 2-year follow-up, respectively, and 91% vs. 79% at 5-year follow-up, respectively; log-rank *P*=0.02) (Figure 3, *panel A*). Similarly, for AVR, the cumulative

Table 2: Echocardiographic parameters in 150 patients with asymptomatic severe aortic stenosis at baseline vs. follow-up divided by symptom status at follow-up echocardiography.

	Symptomatic at follow-up (N = 78)			**Asymptomatic at follow-up (N = 72)**			***P* value intergroup**	
Variable	**Baseline**	**Follow-up**	***P* value**	**Baseline**	**Follow-up**	***P* value**	**Baseline**	**Follow-up**
Aortic valve								
Mean gradient (mmHg)	38.4±11.6	49.0±15.8	**<0.001**	39.4±13.5	46.6±15.8	**<0.001**	0.71	0.31
Peak velocity (m/s)	3.9±0.6	4.4±0.6	**<0.001**	4.0±0.6	4.3±0.6	**<0.001**	0.36	0.25
Area (cm^2)	0.88±0.1	0.76±0.1	**<0.001**	0.85±0.1	0.79±0.1	0.05	0.12	0.30
Area index (cm^2/m^2)	0.48±0.1	0.41±0.1	**<0.001**	0.46±0.1	0.42±0.1	**0.02**	0.08	0.41
Stroke volume (ml)	81.1±14.6	80.6±14.8	0.17	81.7±19.5	82.1±19.2	0.71	0.97	0.91
Stroke volume index (ml/m^2)	44.6±9.0	43.7±8.5	0.34	43.6±10.1	43.5±8.3	0.94	0.55	0.84
Left ventricular								
Mass index (g/m^2)	114.0±27.1	129.6±29.2	**<0.001**	113.7±30.6	121.0±29.6	0.009	0.76	0.06
Ejection fraction (%)	61.4±6.3	61.6±6.9	0.25	61.0±5.0	59.5±8.2	0.28	0.65	0.06
GLS (%)	-17.7±2.6	-16.3±2.9	**<0.001**	-18.2±2.6	-16.4±2.6	**<0.001**	0.21	0.83

AVR, aortic valve replacement; GLS, global longitudinal strain; LV, left ventricular.

event rates were significantly higher in patients with impaired baseline LV GLS (>-18.2%) compared with patients with more preserved baseline LV GLS (≤-18.2%) after 2 years (66% vs. 57%, respectively) and 5 years of follow-up (96% vs. 82%, respectively; log-rank *P*=0.03) (Figure 3, *panel B*). The spline curves to assess the association between symptom development and aortic valve intervention across a range of LV GLS are shown in Supplemental Figure 4. For both symptom development and aortic valve intervention, the linearity assumption was not violated (χ^2, 0.83; *P*=0.67, and χ^2, 1.86; *P*=0.41, respectively). For symptom development, a plateau can be seen (Supplemental Figure 4). For aortic valve intervention, a clear increase in hazard ratios can be observed for more impaired LV GLS (Supplemental Figure 4).

DISCUSSION

THIS study demonstrated that in patients with asymptomatic severe AS and preserved LVEF, LV GLS assessed by speckle tracking imaging is impaired as compared with age- and sex matched controls without structural heart disease. Over time, patients with asymptomatic severe AS showed a progression of AS severity accompanied by increasing LV hypertrophy and further impairment of LV GLS, while LVEF remained relatively unchanged. Patients with impaired LV GLS at baseline showed a higher risk for developing symptoms and for needing aortic valve intervention at follow-up as compared with patients with more preserved LV GLS. These findings suggest that LV GLS is a more sensitive marker for early myocardial damage than LVEF in this patient group and may help identify the patients who may benefit from earlier AVR.

LV GLS AS A MARKER FOR SUBTLE LV DYSFUNCTION IN ASYMPTOMATIC SEVERE AS

Symptom development and LV systolic dysfunction are the main factors that determine the timing of AVR in patients with severe AS [1, 2]. However, decreased physical activity in the aging AS population may result in the underrecognition or late reporting of symptoms [18]. Zilberszac et al. [19] demonstrated that 43% of elderly patients with asymptomatic severe AS who developed symptoms presented with severe heart failure symptoms (New York Heart Association class ≥III). The deterioration of LV systolic function defined by an LVEF <50% can be regarded as a more objective parameter that indicates the need for AVR. However, this will only occur when the concentric remodeled left ventricle fails to maintain normal wall stress because of significant afterload mismatch [20]. At this stage, LV remodeling is characterized by progressive myocardial fibrosis, which is not reversible after an intervention [21, 22]. Therefore, more sensitive markers of LV systolic dysfunction are needed at an earlier stage to identify patients with severe AS who are at risk for irreversible myocardial damage. Recently, Stokke et al. [12] showed that by inducing concentric LV remodelling with an increase in wall thickness and a reduction in diameter of the LV cavity, the LVEF can remain preserved, whereas LV GLS will be impaired. While the presence of impaired LV GLS with preserved LVEF has been described in symptomatic severe AS [8, 9, 23], the prevalence of impaired LV GLS in asymptomatic severe AS has been less studied. Lafitte et al. [24] reported significantly impaired LV GLS in 65 patients with asymptomatic severe AS compared with 60 healthy participants (-

17.8±3.5% vs. -21.1±1.8%, respectively; P <0.05), while no differences were observed in LVEF (64±7% vs. 66±5%, respectively) [24]. This study extends these findings in a larger population. However, the mean value of LV GLS in this study was more preserved than that reported in previous studies (-18.0% vs. -15% to -16.6%) [25–29]. This discrepancy could be explained by the inclusion of older patients in those studies. Furthermore, to our knowledge, this study is the first to report sequential measurements of LV GLS in the period between the initial AS diagnosis and intervention and to demonstrate a clear deterioration of LV GLS without a decline in LVEF.

Prognostic value of LV GLS in patients with asymptomatic severe AS

Multiple echocardiographic predictors of mortality and other adverse cardiac events have been identified in asymptomatic severe AS with preserved LVEF (i.e., peak aortic jet velocity >5.0 m/s [4, 19, 30, 31], aortic valve calcification [27, 32], small AVA [33], inappropriate LV hypertrophy [34], and increased valvuloarterial impedance [35]. Data demonstrating the prognostic effect of LV GLS in severe AS and its incremental value over these determinants are accumulating. In a cohort of 395 patients with AS, including 302 patients with severe AS, Kusunose et al. [10] demonstrated that LV GLS was an independent predictor of all-cause mortality and had incremental prognostic value on top of known echocardiographic predictors and symptom status. However, only 21% of these patients with severe AS were asymptomatic, and mortality rates were high (25%). Lancellotti et al. [25] showed in 163 exclusively asymptomatic patients with severe AS that LV GLS was independently associated with the occurrence of cardiac events (i.e., symptom development, eventual AVR, and death). Other studies have investigated the prognostic effect of LV GLS in asymptomatic AS, but these often had small patient samples, included moderate AS, or did not report symptom development as an end point [6, 26–29]. In contrast, this study included a larger study population of 220 patients with asymptomatic severe AS with low mortality rates at follow-up (28 patients [13%]) and a more preserved LV GLS at baseline, thus representing a lower-risk study population in an earlier disease stage of severe AS. In addition, this study demonstrated that the natural course of LV GLS is characterized by further deterioration over time. These results provide further insights into the currently available literature by confirming that LV GLS is a sensitive marker for subclinical myocardial dysfunction and might aid in identifying patients who are at risk for symptom development and the need for intervention. Therefore, the present evaluation corroborates that LV GLS holds promise in the pre-operative assessment of patients with asymptomatic severe AS without overt signs of LV dysfunction, although further prospective research is needed to determine the exact role of LV GLS in predicting AS progression and severity.

Clinical implications

In patients with symptomatic severe AS, it has been demonstrated that myocardial fibrosis can be present and persist after AVR [21]. Diffuse myocardial fibrosis that was noninvasively assessed by native T1 mapping on cardiac magnetic resonance imaging was present in asymptomatic patients with severe AS and was associated with LV GLS that was measured by speckle tracking echocardiography [36]. This study shows that LV

GLS is often impaired in asymptomatic severe AS and will further deteriorate if left untreated, while LVEF remains unchanged. This suggests that patients with impaired LV GLS at baseline have subclinical myocardial dysfunction that is probably secondary to diffuse fibrosis, which is not detected by the conventional echocardiographic parameters of LV systolic function. Therefore, the evaluation of LV GLS and consideration of objective signs of AS-related cardiac damage in patients with asymptomatic severe AS with preserved LVEF (as recently suggested in a new AS staging classification [37]) may help to define the optimal timing for AVR (before symptom development and irreversible myocardial damage occur).

LIMITATIONS

This study was limited by its retrospective design, which could have introduced a selection bias. Left ventricular GLS was measured using different platforms, which can lead to slight variations in the quantification of LV systolic dysfunction when considering the current variability in LV GLS measurements across vendors. Although intervendor differences in LV GLS measurements have been reported to be statistically significant, this bias was only moderate and the interobserver and intraobserver reproducibility of LV GLS were comparable with or superior to conventional echocardiographic parameters, such as LVEF [38, 39]. Furthermore, the precision of LV GLS has been shown to be high even in observers with low experience levels [39]. The differences in mean LV GLS values or in the prevalence of LV systolic dysfunction based on an LV GLS value >-19.6% were not observed across the participating centers. Finally, as the participating centers are tertiary referral hospitals for AVR, referral bias could be present, with subsequent increased rates of AVR. The decision of referral for AVR was left to the discretion of the treating cardiologist.

CONCLUSIONS

IN asymptomatic severe AS, most patients have impaired LV GLS at the initial diagnosis despite preserved LVEF. Furthermore, during follow-up and before intervention, a further deterioration of LV GLS occurred without a change in LVEF, whereas AS severity progressed and LV hypertrophy increased. Impaired LV GLS at baseline was associated with a higher risk of symptom development and need for aortic valve intervention. Therefore, assessing LV GLS holds promise in the risk assessment of asymptomatic severe AS, although further prospective studies in larger patient populations are warranted to establish the exact role of LV GLS, integrated with other markers of AS severity and progression, in identifying patients who might benefit from earlier aortic valve intervention.

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SUPPLEMENTARY MATERIAL

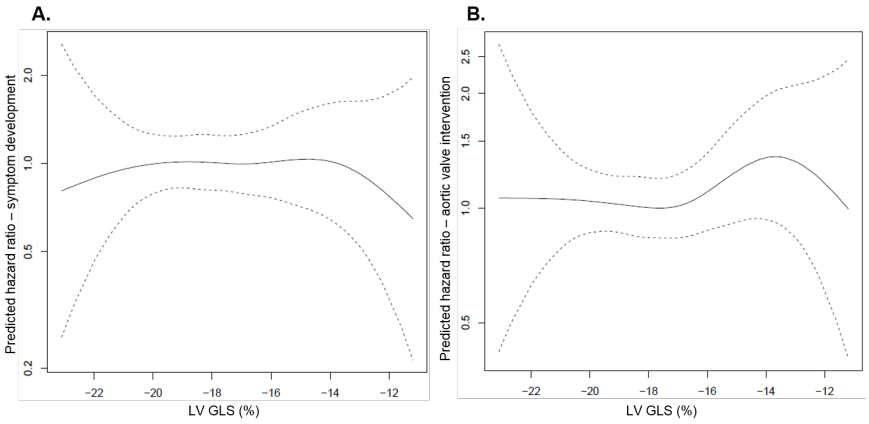

Figure 4: Predicted outcomes of asymptomatic severe aortic stenosis across a range of left ventricular (LV) global longitudinal strain (GLS). Fitted Cox spline models, including overlaying confidence intervals, for symptom development (*panel A*) and aortic valve intervention (*panel B*) vs. LV GLS after adjustment for age, sex, coronary artery disease, atrial fibrillation and LV mass index.

Table 3: Changes in valve hemodynamics and left ventricular (LV) systolic function in 150 patients with asymptomatic severe aortic stenosis from baseline to follow-up (second transthoracic echocardiogram at last follow-up or prior to aortic valve replacement).

Variables	**Baseline (N = 150)**	**Follow-up (N = 150)**	***P* value**
Aortic valve mean gradient (mmHg)	38.9±12.5	47.8±15.8	**<0.001**
Aortic valve peak velocity (m/s)	3.9±0.6	4.4±0.6	**<0.001**
Aortic valve area (cm^2)	0.87±0.1	0.78±0.1	**<0.001**
Aortic valve area index (cm^2/m^2)	0.47±0.1	0.42±0.1	**<0.001**
Stroke volume (ml)	81.4±17.1	81.3±17.0	0.16
Stroke volume index (ml/m^2)	44.1±9.5	43.6±8.4	0.37
LV mass index (g/m^2)	113.9±28.7	125.4±29.6	**<0.001**
LV ejection fraction (%)	61.2±5.7	60.6±7.6	0.15
LV global longitudinal strain (%)	-18.0±2.6	-16.3±2.8	**<0.001**

LV, left ventricular.

Table 4: Baseline clinical and echocardiographic characteristics of asymptomatic severe aortic stenosis patients divided according to the median value of LV GLS at baseline ≤ −18.2% (more preserved) vs. >-18.2% (more impaired).

Variables	Total population of AS patients (N = 220)	Preserved LV GLS (≤-18.2%) (N = 118)	Impaired LV GLS (>-18.2%) (N = 102)	*P* value
Clinical characteristics				
Age (years)	67.9±13.0	66.8±14.4	69.2±11.2	0.16
Male gender, *N* (%)	126 (57)	61 (52)	65 (64)	0.07
Body surface area (m^2)	1.87±0.2	1.85±0.2	1.89±0.2	0.14
Hypertension, *N* (%)	128 (59)	64 (55)	64 (63)	0.20
Hypercholesterolemia, *N* (%)	103 (47)	49 (42)	54 (54)	0.09
Diabetes, *N* (%)	34 (16)	19 (16)	15 (15)	0.78
History of smoking, *N* (%)	73 (38)	40 (36)	33 (41)	0.49
Coronary artery disease, *N* (%)	47 (22)	17 (15)	30 (30)	**0.007**
Prior myocardial infarction, *N* (%)	15 (7)	5 (4)	10 (10)	0.10
History of atrial fibrillation, *N* (%)	40 (18)	14 (12)	26 (26)	**0.009**
Medication use, *N* (%)				
Beta-blocker	78 (36)	35 (30)	43 (43)	0.05
ACE-inhibitor/ARB	88 (40)	43 (37)	45 (45)	0.24
Calcium antagonist	48 (22)	26 (22)	22 (22)	0.94
Diuretic agents	52 (24)	29 (25)	23 (23)	0.70
Statins	112 (51)	54 (46)	58 (57)	0.10
Aspirin and/or clopidogrel	93 (43)	46 (39)	47 (47)	0.28
Vitamin K antagonist or NOAC	31 (14)	17 (15)	14 (14)	0.89
Creatinin level (µmol/l)	80 [70-97]	76 [69-93]	85 [73-104]	**0.006**
Estimated GFR (ml/min/1.73 m^2)	76 [61-89]	79 [68-91]	72 [55-88]	**0.04**

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; AS, aortic stenosis; GFR, glomerular filtration rate estimated using CKD-EPI formula; GLS, global longitudinal strain; LV, left ventricular; NOAC, novel oral anti-coagulants.

Table 4: Baseline clinical and echocardiographic characteristics of asymptomatic severe aortic stenosis patients divided according to the median value of LV GLS at baseline ≤ −18.2% (more preserved) vs. >-18.2% (more impaired) (*continued*).

Variables	Total population of AS patients (N = 220)	Preserved LV GLS (≤-18.2%) (N = 118)	Impaired LV GLS (>-18.2%) (N = 102)	*P* value
Baseline echocardiography				
Valve anatomy, *N* (%)				0.18
Tricuspid	170 (77)	87 (74)	83 (81)	
Bicuspid	50 (23)	31 (26)	19 (19)	
Aortic valve mean gradient (mmHg)	39.4±12.6	38.2±12.3	40.8±12.9	0.13
Aortic valve peak velocity (m/s)	4.0±0.6	3.9±0.6	4.0±0.6	0.39
Aortic valve area (cm^2)	0.86±0.1	0.87±0.1	0.85±0.1	0.21
Aortic valve area index (cm^2/m^2)	0.46±0.1	0.47±0.1	0.45±0.1	**0.008**
Stroke volume (ml)	81.4±17.1	80.9±16.0	82.0±18.4	0.64
Stroke volume index (ml/m^2)	43.8±9.1	44.4±9.6	43.1±8.6	0.31
LV end-diastolic diameter (mm)	45.4±5.8	44.6±5.5	46.5±6.0	0.02
LV end-systolic diameter (mm)	28.2±5.0	27.1±4.4	29.5±5.5	**0.001**
Intraventricular septal thickness (mm)	12.9±2.3	12.7±2.1	13.1±2.5	0.23
Posterior wall thickness (mm)	11.6±1.9	11.4±1.8	11.8±1.9	0.10
LV mass index (g/m^2)	112.0±27.7	107.1±25.9	117.7±28.7	**0.006**
LV ejection fraction (%)	61.5±5.9	62.5±5.5	60.4±6.3	**0.008**
LV global longitudinal strain (%)	-17.9±2.5	-19.8±1.1	-15.8±1.8	**<0.001**

AS, aortic stenosis; GLS, global longitudinal strain; LV, left ventricular.