Usefulness of Global Left Ventricular Longitudinal Strain for Risk Stratification in Low Ejection Fraction, Low-Gradient Aortic Stenosis

Results From the Multicenter True or Pseudo-Severe Aortic Stenosis Study

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Background—The objective of this study was to examine the impact of left ventricular (LV) global longitudinal strain (GLS) measured at rest and at dobutamine stress echocardiography on the outcome of patients with low LV ejection fraction and low-gradient aortic stenosis.

Methods and Results—Among the 202 patients with low LV ejection fraction (≤40%), low-gradient aortic stenosis (mean transvalvular gradient <40 mmHg and indexed aortic valve area ≤0.6 cm²/m²) prospectively enrolled in the multicenter True or Pseudo-Severe Aortic Stenosis study, 126 patients with resting GLS and 73 patients with stress GLS available were included in this substudy. Three-year survival rate was 49% in patients with rest GLS <9% compared with 68% in patients with GLS >9% (P=0.02). In a multivariable Cox model adjusted for age, coronary artery disease, projected aortic valve area at a normal flow rate and type of treatment (aortic valve replacement versus conservative), rest GLS <9% (hazard ratio, 2.18; P=0.015) remained independently associated with all-cause mortality. GLS <10% measured during dobutamine stress echocardiography was also independently associated with mortality (hazard ratio, 2.67; P=0.01). In the subset of patients with stress GLS (n=73), the χ² of the multivariable model to predict all-causes mortality was 21.96 for stress GLS versus 17.78 for rest GLS.

Conclusions—GLS is independently associated with mortality in patients with low LV ejection fraction, low-gradient aortic stenosis. Stress GLS measured during dobutamine stress echocardiography may provide incremental prognostic value beyond GLS measured at rest. Hence, measurement of GLS at rest and during dobutamine stress echocardiography may be helpful to enhance risk stratification in low LV ejection fraction, low-gradient aortic stenosis.

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Key Words: aortic valve stenosis • echocardiography, stress • longitudinal strain • low flow • low gradient • outcome measures

Although patients with left ventricular (LV) systolic dysfunction and low-gradient (LG) aortic stenosis (AS) represent only 5% to 10% of AS patients,1 they also constitute one of the most challenging subsets of AS patients with respect to diagnosis and treatment. These patients indeed have a poor prognosis with conservative therapy, but a high-operative mortality if treated surgically.2,3 Dobutamine stress echocardiography (DSE) has been shown to be helpful for risk stratification and therapeutic decision making in patients with low LV ejection fraction (LVEF), LG AS.4,5,6 The assessment of LV flow reserve (ie, increase in stroke volume) during DSE has been shown to be useful to predict operative mortality but not to predict late mortality or recovery of LV function after aortic valve replacement (AVR).2,3 Furthermore, AS severity as documented by the projected aortic valve area at normal flow rate (AVAproj)0.61 and peak stress LVEF independently predict overall mortality in these patients with low LVEF; LG AS.4 However, LVEF is largely influenced by LV geometry
and preload and may thus lack sensitivity to assess the presence and severity of myocardial systolic dysfunction. Recent studies suggest that LV global longitudinal strain (GLS) may be a more sensitive marker of intrinsic myocardial function than LVEF in patients with AS and preserved LVEF. There is however limited data about the prognostic value of GLS in patients with low LVEF, LG AS. In a previous substudy of the True or Pseudo-Severe Aortic Stenosis (TOPAS) study, Bartko et al. reported the data from 1 center suggesting that longitudinal strain parameters measured during DSE were associated with increased risk of mortality independently of LVEF and B-type natriuretic peptide.

The objective of the present study was thus to evaluate in a prospective cohort of patients with low LVEF, LG AS recruited in the TOPAS multicenter study, the prognostic value of GLS measured at rest and dobutamine stress.

### Methods

#### Study Protocol

The protocol of the TOPAS multicenter prospective observational study has been described in detail in our previous publications. Briefly, between July 2002 and March 2011, we recruited 202 patients with LG AS (mean gradient <40 mmHg and indexed AVA ≤0.6 cm²/m²) with reduced LVEF (≤40%). Patients were excluded if they had more than mild aortic regurgitation, moderate mitral regurgitation, or mild mitral stenosis.

Clinical Data

Clinical data included age, sex, height, weight, body surface area (BSA), systolic and diastolic blood pressure, documented diagnosis of traditional cardiovascular risk factors such as hypertension, diabetes mellitus, dyslipidemia, smoking, chronic obstructive pulmonary disease, coronary artery disease (CAD: history of myocardial infarction or coronary artery stenosis ≥50% on coronary angiography), and logistic EuroSCORE. Medication was recorded at the time of echocardiography.

Doppler Echocardiography

At entry in the study, all patients underwent a comprehensive echocardiography using commercially available equipment (IE33, Philips or Vivid 7, GE Healthcare) at rest and during dobutamine stress as previously described. The dobutamine infusion protocol consisted of 8-minute increments of 2.5 to 5 μg/kg per minute up to a maximum dosage of 20 μg/kg per minute. Continuous-wave Doppler of the aortic valve velocity spectrum, as well as pulsed-wave Doppler of the LV outflow tract velocity spectrum, was recorded at rest and at each step of the dobutamine protocol. For the 2-dimensional images of the LV, a minimum of 3 consecutive cycles were recorded from the standard parasternal and apical views at each stage of the DSE protocol. LVEF was measured by the biplane Simpson method. Stroke volume was measured in the LV outflow tract and indexed for body surface area. SVi was calculated as the average of longitudinal strain of the 2-, 3-, and 4-chamber apical views, at rest and at DSE. Rest GLS was available in 126 patients (62%) of the patients included in the TOPAS study and stress GLS in 73 (58%) of the 126 remaining patients (Figure 1). The major causes of missing GLS were poor quality of image (poor echogenicity and inadequate frame rate; ie, <50 fps²). GLS data were expressed in absolute value (°%). Delta GLS was calculated as the difference between stress and rest GLS. Intra- and interobserver variability of GLS was 6% and 7.5%, respectively. Intraclass correlation coefficient was 0.94 for intraobserver GLS measurements and 0.86 for interobserver measurements.

#### Statistical Analysis

The primary end point for this study was all-cause mortality. Results are expressed as means±SD or percentages unless otherwise specified. Spline curve analyses were performed to identify the rest and stress GLS cutoff values related to the absolute risk of mortality in our series (ie, relative risk of 1). Differences between patients with GLS >9% and GLS <9% or stress GLS >10% and stress GLS <10% (ie, best cutoff values on spline curve analysis) were compared with the use of the t test or the Wilcoxon rank-sum test for continuous variables and the χ² test or Fisher exact test for categorical variables as appropriate. Correlations between continuous variables were determined using Pearson method. Paired t test was used to assess change in GLS under dobutamine stress. Kaplan–Meier curves and log-rank test of the time-to-event data were used to assess the effect of rest and stress GLS on all-cause mortality in the whole cohort and in the subset of patients treated with AVR and those treated conservatively (ie, no-AVR). The effect of the clinical and Doppler-echocardiographic variables on survival was assessed with the use of Cox proportional hazard models. All the variables with a P value of <0.10 in univariable analysis were incorporated into the multivariable model. A P value of <0.05 was considered statistically significant.

#### Results

Baseline Patient Characteristics

Baseline characteristics of the subset of 126 patients with rest GLS data available (Figure 1) are shown in Table 1 and were...
Patients with rest GLS data available had a higher proportion of men and a higher prevalence of smoking compared with those with missing GLS data (Table II in the Data Supplement). However, outcome was similar in both subsets (3-year mortality: 43±4% versus 46±5%; *P*=0.60). Among the 126 patients included in the present study (Table 1), mean age was 72±9 years, patients were more frequently men (83%), and 48% had New York Heart Association function class ≥III. Prevalence of CAD was 68%, hypertension 62%, and diabetes similar to those of the whole TOPAS cohort (Table I in the Data Supplement).
mellitus was 33%. Baseline AVA was 0.85±0.25 cm², mean gradient 24±9 mm Hg, AVAproj 1.00±0.20 cm², LVEF 28±8%, and rest GLS [9.4±3.0]%.

Sixty seven (53%) underwent AVR within 3 months of enrollment and the remaining patients were treated conservatively. Among AVRrs, 57 (85%) were surgical (32 with concomitant coronary artery bypass graft surgery) and 10 (15%) were transcatheter. The therapeutic decision (AVR or medical management) was left to the discretion of the treating physicians.

Comparison of Patients Characteristics According to Rest GLS

A spline curve representing the risk of mortality according to rest GLS was used to identify the cutoff value of GLS associated with increased risk of mortality (ie, relative risk >1). The spline curve crossed the relative risk of mortality of 1 at a GLS of 9.38% (Figure I in the Data Supplement). The cohort was thus dichotomized according to the closest rounded value of GLS (ie, < or >9%).

Patients with GLS <9% had similar demographics and clinical data compared with those with GLS >9%, except for heart rate that was significantly higher in patients with lower GLS (Table 1). With regard to Doppler-echocardiographic data, patients with GLS <9% have larger LV end-systolic diameter (52±11 versus 47±8 mm; P=0.03), lower SVi (28±10 versus 34±8 mL/m²; P=0.0002), and lower LVEF (23±6 versus 33±6%; P<0.0001) when compared with those with GLS >9%. However, there was no significant difference in AS severity between the 2 groups.

Correlates of Rest and Stress GLS

Rest GLS correlated with LVEF (r=0.73; P<0.0001) and SVi (r=0.36; P<0.0001) as well as with stress GLS (r=0.74; P<0.0001; Figures II and III in the Data Supplement). GLS increased significantly from rest to peak DSE (rest, 9.2±3.0 versus stress, 10.2±3.4%; P<0.0001; Figures II and III in the Data Supplement). GLS also remained independently associated with mortality (GLS <|9.%: HR, 2.71; 95% CI, 1.11–6.94; P=0.029) after adjustment for type of treatment (ie, aortic valve replacement [AVR] vs conservative; ie, no AVR). *P<0.05 vs GLS >9%+AVR. †P<0.05 vs GLS >9%+AVR, GLS <|9.%+AVR and GLS >9%+no AVR. §P<0.05 vs GLS >9%+no AVR. ¥P<0.05 vs GLS <9%+no AVR. The numbers at the bottom of the graph represent the number of patients at risk at each follow-up year. The P value is that of the log-rank test. HR indicates hazard ratio.
adjustment for heart rate. The adjustment for $\beta$-blocker therapy did not change the results. Rest LVEF was significantly ($P=0.02$) associated with mortality in univariable analysis but not in multivariable analysis. There was a trend for association between SVi and mortality in univariable analysis ($P=0.10$) and no association in multivariable analysis. GLS provided significant incremental prognostic value beyond that obtained with LVEF and other baseline risk factors (Figure IV in the Data Supplement).

The presence of CAD ($P=0.02$), multivessel coronary disease ($P=0.0009$), and history of myocardial infarction ($P=0.0018$) were all associated with mortality in univariable analysis. However, GLS $<|9|\%$ remained associated with mortality even after further adjustment for CAD (HR, 2.18; 95% CI, 1.16–4.10; $P=0.015$; Table 2), multivessel disease (HR, 2.47; 95% CI, 1.30–4.77; $P=0.006$), or history of myocardial infarction (HR, 2.19; 95% CI, 1.17–4.14; $P=0.015$).

When using GLS in continuous format instead of dichotomous format (ie, $<|9|\%$), the univariable and multivariable associations with mortality were similar or stronger (Table 2).

### Thirty-Day Mortality According to Rest GLS in Patients Treated by AVR

Thirty-day mortality after AVR was 9% (6 deaths): 5 deaths occurred in the group of patients with GLS $<|9|\%$ when compared with 1 in those with GLS $>|9|\%$ (16.7% versus 2.7% 30-day mortality rate, respectively; $P=0.08$). When we analyzed only late survival (ie, after exclusion of the 6 deaths occurring in the 30 days after AVR), there was no significant difference in survival between patients with GLS $>|9|\%$ ($83\pm7\%$ versus $79\pm11\%$; $P=0.80$).

### Survival According to Stress GLS

The baseline characteristics and mortality rates (3-year mortality: 46±6\% versus 43±5\%; $P=0.89$) were similar in the subset of patients (n=73) with stress GLS available versus those without stress GLS available (n=126; Table I in the Data Supplement). In this subset, 3-year survival was 74±8\% in patients with stress GLS $>||0|\%$ (cutoff value intersecting the relative risk of 1 on the spline curve; Figure I in the Data Supplement) when compared with 30±10% in patients with stress GLS $<|10|\%$ ($P=0.011$; Figure 3A). Table III in the Data Supplement shows the comparison of baseline characteristics in patients with stress GLS $<|10|\%$ versus those with stress GLS $>|10|\%$. In the patients treated conservatively (n=46), those with stress GLS $>|10|\%$ had better survival than those with stress GLS $<|10|\%$ ($60\pm19\%$ versus $17\pm10\%; P=0.02$; Figure 3B). The subset of patients treated by AVR was too small (n=27) to allow statistical comparison according to stress GLS in this subset. There was a trend for association between stress LVEF ($P=0.08$) and stress SVi ($P=0.06$) with increased mortality in univariable analysis.

After adjustment for type of treatment, stress GLS $<|10|\%$ remained significantly associated with all-cause mortality (HR, 3.06; 95% CI, 1.43–7.10; $P=0.003$; Table 2). After further adjustment for age, CAD, and $AVA_{proj}$, stress GLS $<|10|\%$ remained independently associated with all-cause mortality (HR, 2.67; 95% CI, 1.24–6.25; $P=0.011$; Table 2, model no. 1). Additional adjustment for stress LVEF provided similar results: stress GLS $<|10|\%$ was still independently associated with all-cause mortality (HR, 2.53; 95% CI, 1.07–6.22; $P=0.035$; Table 2, model no. 2) but stress LVF ($P=0.77$) was not. In the subset of patients with stress GLS available (n=73), the multivariable model with stress GLS was superior to the model with rest GLS to predict all-cause mortality ($\chi^2=21.96$ versus 17.78). The univariable and multivariable associations with mortality were similar with stress GLS entered in continuous format versus in dichotomous format (Table 2).

The dobutamine stress–induced change in GLS (ie, stress GLS–rest GLS) was also significantly associated with mortality in univariable analysis ($P=0.03$) and did not reach statistical significance after multivariable adjustment ($P=0.20$). LV flow reserve (ie, increase in SV $\geq 20\%$ under DSE) was not associated mortality in both univariable and multivariable analysis ($P=0.52$ and 0.24, respectively).
Indeed, longitudinal function is a better marker to the LVEF to assess intrinsic myocardial function in patients. Parameters of LV longitudinal function may be superior in patients with low LVEF, LG AS.10,11

The main findings of the present study are (1) low rest and stress GLS are independently associated with all-cause mortality in patients with low LVEF, LG AS, even after adjustment for clinical factors and standard echocardiographic parameters of AS severity and LV function; (2) low GLS is a strong risk factor for mortality in patients treated conservatively as well as in those treated by AVR; (3) stress GLS seems to be superior to rest GLS to predict outcomes in these patients. This is the first multicenter study with centralized analysis of strain parameters in a Echocardiography Core Laboratory to demonstrate the usefulness of rest and stress GLS to predict outcomes in patients with LG AS.

**Prognostic Value of Rest GLS in Low EF, LG AS**

The main challenge in patients with AS and depressed LVEF is to distinguish between true severe versus pseudosevere stenosis and to accurately assess the severity of myocardial impairment, an important determinant of patient prognosis.1 We previously reported that the projected AVA at normal flow rate is superior to standard rest or stress echocardiographic parameters to identify true-severe stenosis and predict outcomes in patients with low LVEF, LG AS.10,11

Besides AS severity and ensuing afterload mismatch, concomitant factors such as CAD, hypertension, and diabetes mellitus may contribute to the development of myocardial fibrosis and dysfunction in AS.14,16,18,21 Previous studies suggest that parameters of LV longitudinal function may be superior to the LVEF to assess intrinsic myocardial function in patients with AS.14,19,20 Indeed, longitudinal function is a better marker than LVEF of the subendocardial function, which is primarily and more severely affected in these patients. Two recent studies reported that LV longitudinal shortening, assessed by mitral ring displacement, is closely related to the extent of myocardial fibrosis, assessed by MRI or myocardial biopsies at the time of AVR.18,19 Furthermore, patients with low LVEF and LG AS had much more advanced myocardial fibrosis and impairment of LV longitudinal function compared with patients with preserved LVEF and high gradient. Several studies have reported that more extensive myocardial fibrosis or its surrogate echocardiographic marker, that is, reduced LV longitudinal shortening, is associated with worse outcomes in AS.15,16,18,21 However, these previous studies did not include, or included small number of, patients with low LVEF, LG AS and most of them were retrospective. In the present study including a prospective cohort of patients with low LVEF, LG AS, we showed that rest GLS is strongly and independently associated with all-cause mortality even after adjustment for concomitant diseases and LV systolic function parameters (ie, LVEF and SVi).

Several factors, besides stenosis severity, may reduce GLS including myocardial ischemia, LV hypertrophy, myocardial fibrosis, concomitant arterial hypertension, etc.19 Hence, GLS is not a specific marker of AS severity per se and, as such, it cannot be used to differentiate true versus pseudosevere stenosis. However, as shown in the present study, this parameter is useful to assess the extent of global LV myocardial impairment, regardless of the causative factor(s), and it can thus contribute to enhance risk stratification in patients with low LVEF LG AS. In patients treated conservatively, low GLS at baseline was associated with a continued increased risk in mortality over time. In patients undergoing AVR, the impact of low GLS was predominantly on the early postoperative phase and there was a trend toward higher 30-day mortality in patients with GLS <|9|% versus those with GLS >|9|%. Hence, these findings suggest that rest GLS could be useful to assess operative risk in patients with low LVEF, LG AS. Further studies in larger group of patients are needed to confirm the use of this parameter for operative risk stratification.

**Prognostic Value of Stress GLS in Low EF, LG AS**

By determining actual stenosis severity and presence/absence of flow reserve, DSE is useful to enhance risk stratification and therapeutic decision making.22,23 The stress GLS performed better than the LV flow reserve, that is, the change in stroke volume, which was not observed to be predictive of prognosis in this population. Although stress GLS correlated well with rest GLS, there was an important interindividual variability

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**Discussion**

The main findings of the present study are (1) low rest and stress GLS are independently associated with all-cause mortality in patients with low LVEF, LG AS, even after adjustment for clinical factors and standard echocardiographic parameters of AS severity and LV function; (2) low GLS is a strong risk factor for mortality in patients treated conservatively as well as in those treated by AVR; (3) stress GLS seems to be superior to rest GLS to predict outcomes in these patients. This is the first multicenter study with centralized analysis of strain parameters in a Echocardiography Core Laboratory to demonstrate the usefulness of rest and stress GLS to predict outcomes in patients with LG AS.

**Figure 3.** Impact of stress global longitudinal strain on all-causes mortality. A. The survival in patients with stress global longitudinal strain (GLS) >|10|% vs those with stress GLS <|10|% and (B) the survival in these groups of patients after further dichotomization for the type of treatment (ie, aortic valve replacement [AVR] vs conservative). $P<0.05$ vs stress GLS <|10|%+no AVR; $P<0.05$ vs stress GLS >|10|%+AVR; $P<0.05$ vs stress GLS >|10|%+no AVR; §$P<0.05$ vs stress GLS <|10|%+AVR. The numbers at the bottom of the graph represent the number of patients at risk at each follow-up year. The $P$ value is that of the log-rank test. HR indicates hazard ratio.

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in stress GLS for a given value of rest GLS (Figure II in the Data Supplement). Furthermore, our results suggest that stress GLS provides significant incremental prognostic value compared with rest GLS. The stress GLS also seemed to be better in predicting mortality than the myocardial contractile reserve as assessed by the change in GLS from rest to peak stress. This finding may be explained by the fact that patients with the same degree of contractile reserve may have different peak stress GLS if they have different rest GLS. The peak stress GLS reflects the maximum LV longitudinal shortening that the LV is able to achieve under stress conditions and it is therefore a composite marker that integrates both the baseline rest longitudinal function and the myocardial reserve.

These results confirm and extend those we obtained in one of the centers participating in the TOPAS study (Vienna General Hospital). In addition, in the present study reporting the results of the multicenter TOPAS cohort, we have been able to perform multivariable analyses with more comprehensive adjustment and thereby confirm the independent association between rest or stress GLS and outcomes. We also demonstrated the superiority of stress GLS versus rest GLS to predict outcomes and we obtained data supporting the usefulness of rest GLS to predict operative mortality in the subset of patients undergoing AVR. Nonetheless, one advantage of rest GLS is that the prognostic information can be obtained without performing DSE. This makes it simple to obtain and more widely available even if there is still some additional benefit to measuring stress GLS.

Clinical Implications

Patients with low LVEF, LG AS often have a poor prognosis with medical therapy but increased operative mortality when treated surgically. Individualized risk stratification is thus essential in these patients and for this purpose, GLS and particularly stress GLS measured during DSE seems superior to other parameters of LV function to predict outcomes in both patients treated conservatively and those treated surgically. Patients under conservative management seems to have markedly increased risk of mortality when they have reduced rest GLS, and even more when they have reduced stress GLS. These patients should thus receive particular attention with optimization of heart failure therapy and close clinical and echocardiographic follow-up. The data of the present study also raise the hypothesis that, among patients undergoing AVR, those with low preoperative GLS may be at higher risk for 30-day mortality, regardless of LVEF, stroke volume index, or flow reserve. Hence, parameters of LV longitudinal function could be useful for operative risk stratification but further studies in larger group of patients are needed to confirm this hypothesis. However, our data suggest that the presence of low GLS at rest and DSE should not preclude consideration for AVR. Indeed, patients with low GLS had even worse prognosis under conservative management than under AVR.

Recent studies suggested that transcatheter aortic valve implantation may provide a valuable alternative to surgical AVR in patients with low LVEF and LG AS. Further studies are needed to determine which is the best procedure, surgical AVR or transcatheter aortic valve implantation, for patients with LG AS having low GLS at rest and during DSE.

Strengths and Limitations of the Study

The population size may have limited our ability to detect significant association with some other risk factors and it does not allow the realization of multivariable analysis for 30-day mortality in the subset of patients undergoing AVR. Some multivariable models for overall mortality were overfitted and so their results should be interpreted cautiously. The statistical power was not sufficient to perform separate multivariable analyses for overall mortality in the subsets of patients treated conservatively or by AVR. However, the association between GLS and mortality remained significant in the whole cohort after adjustment for the type of the treatment in the multivariable models.

In the TOPAS study, we used a low-dose (≤20 μg/kg per minute) DSE protocol as it is generally recommended for LG AS patients. It is however unlikely that the increase in GLS would have been magnified with higher dose (≤40 μg/kg per minute) protocol. Indeed, the inotropic reserve, if any, generally occurs at low dobutamine doses and the utilization of higher dose in the AS population might, in fact, induce a decrease in GLS after initial increase at low dose because of tachycardia and impaired LV filling as well as occurrence of myocardial ischemia. Furthermore, a high-dose protocol may be associated with serious adverse effects in such population.

GLS data were not available in a substantial proportion of the patients recruited in the TOPAS study because of inadequate image quality and low frame rate. However, most of the baseline characteristics as well as mortality rates were similar in patients with versus without GLS data available (Table II in the Data Supplement). So, it is unlikely that this limitation may have introduced an important selection bias. Furthermore, this remains the largest study reporting GLS data in low LVEF, LG AS. With the technology available nowadays for the acquisition of LV cineloops at high frame rate, it is expected that the feasibility of GLS measurements at rest and DSE would be ≥90% and 80%, respectively.

Given that platforms from different vendors may provide different results for myocardial strain, it was thus important, in the context of this multicenter study, to perform the GLS measurements centrally using the same platform to minimize intersite variability. However, the limitations of this approach are that these measurements are performed with DICOM files instead of raw data files and that the speckle-tracking algorithm used by the TomTec platform is different from that used by the other platforms (eg, EchoPac or QLab). These limitations may somewhat decrease the accuracy of the GLS measurements. Nevertheless, the strain measurements with the TomTec platform have been well validated in previous studies and, in the present study, GLS measured with this platform was strongly associated with outcome. Further studies are needed to validate the cut points of rest and stress GLS proposed in this study and to determine whether these cut points should be adjusted according to the type of treatment (conservative versus AVR), the type of end point (30-day versus late mortality), or the platform used for strain measurements.

Given the strong collinearity between rest and stress GLS, it was not possible to include both parameters in the same multivariable models. However, when using the same subset of
patients and the same adjustment for the multivariable analysis, the \( \chi^2 \) of the multivariable model for prediction of all-cause mortality was better with stress GLS than with rest GLS.

**Conclusions**

In this prospective series of patients with low LVEF, LG AS, GLS has been shown to be strongly and independently associated with all-cause mortality, particularly in patients treated conservatively. The results of this study suggest that GLS may be useful to predict operative mortality in patients undergoing AVR as well as both short- and long-term risk of mortality in patients treated conservatively. Finally, stress GLS measured during DSE may provide incremental prognostic value beyond GLS measured at rest. Further studies are needed to determine whether transcatheter aortic valve implantation should be preferred to surgical AVR in patients with LG AS having low GLS at rest and during DSE.

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**Disclosures**

None.

**References**


Patients with low left ventricular ejection fraction, low-gradient aortic stenosis often have a poor prognosis with medical therapy but increased operative mortality when treated surgically. Risk stratification is thus crucial in this population. For this purpose, global longitudinal strain (GLS) and particularly stress GLS measured during dobutamine stress echocardiography seems superior to other parameters of left ventricular function to assess degree of myocardial impairment and predict outcomes in both patients treated conservatively and those treated surgically. Patients under conservative management have markedly increased risk of mortality when they have reduced rest GLS (<9%), and even more when they have reduced stress GLS (<10%). These patients should thus receive particular attention with optimization of heart failure therapy and close clinical and echocardiographic follow-up, and aortic valve replacement (AVR) should be reconsidered if aortic stenosis is severe. The data of the present study also suggest that, among patients undergoing AVR, those with low preoperative GLS (<9%) may be at higher risk for 30-day mortality. Hence, parameters of left ventricular longitudinal function assessed by speckle tracking could be useful for operative risk stratification but further studies in larger number of patients are needed to confirm this hypothesis. However, the presence of low GLS at rest and at dobutamine stress echocardiography should not preclude consideration for AVR. Indeed, patients with low GLS had even worse prognosis under conservative management than under AVR. Transcatheter aortic valve implantation may provide a valuable alternative to surgical AVR in patients with low left ventricular ejection fraction and low-gradient aortic stenosis but this remains to be confirmed in future studies.
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Usefulness of Global Left Ventricular Longitudinal Strain for Risk Stratification in Low Ejection Fraction, Low-Gradient Aortic Stenosis: Results From the Multicenter TOPAS Study


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### Table S1. Baseline Clinical and Doppler-echocardiographic Characteristics in the Whole Cohort and in the Subcohorts with Rest GLS and Stress GLS Data Available

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</thead>
<tbody>
<tr>
<td><strong>Demographics and Physical Exam</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>73.0±10.0</td>
<td>72±9</td>
<td>71.0±9.8</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>157(78)</td>
<td>104(83)</td>
<td>59(81)</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>1.84±0.21</td>
<td>1.85±0.2</td>
<td>1.87±0.22</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>71±15</td>
<td>71±13</td>
<td>72±14</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>120±18</td>
<td>120±18</td>
<td>119±21</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>72±10</td>
<td>71±10</td>
<td>71±11</td>
</tr>
<tr>
<td>NYHA functional class ≥III, n (%)</td>
<td>103(51)</td>
<td>61(48)</td>
<td>28(38)</td>
</tr>
<tr>
<td><strong>Risk factors and concomitant diseases</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>127(63)</td>
<td>78(62)</td>
<td>42(58)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>71(35)</td>
<td>42(33)</td>
<td>30(41)</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>143(71)</td>
<td>89(71)</td>
<td>50(68)</td>
</tr>
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<td>Smoking, n (%)</td>
<td>122(60)</td>
<td>84(67)</td>
<td>48(66)</td>
</tr>
<tr>
<td>Coronary artery disease, n (%)</td>
<td>140(69)</td>
<td>86(68)</td>
<td>46(63)</td>
</tr>
<tr>
<td>Multi-vessel coronary disease, n (%)</td>
<td>105(52)</td>
<td>62 (49)</td>
<td>36(49)</td>
</tr>
<tr>
<td>Number of diseased coronary vessels, n*</td>
<td>2.3±0.9</td>
<td>2.2±0.9</td>
<td>2.3±0.9</td>
</tr>
<tr>
<td>Previous coronary artery bypass graft, n (%)</td>
<td>57(35)</td>
<td>34(27)</td>
<td>22(30)</td>
</tr>
<tr>
<td>Previous myocardial infarction, n (%)</td>
<td>109(54)</td>
<td>70(56)</td>
<td>42(58)</td>
</tr>
<tr>
<td>Concomitant coronary artery bypass graft, n (%)</td>
<td>52(26)</td>
<td>35 (28)</td>
<td>14(19)</td>
</tr>
<tr>
<td>Number of grafted coronary vessel, n**</td>
<td>2.1±1.9</td>
<td>2.0±1.1</td>
<td>1.9±0.9</td>
</tr>
<tr>
<td>COPD, n (%)</td>
<td>56(28)</td>
<td>33(26)</td>
<td>17(23)</td>
</tr>
<tr>
<td>Logistic EuroSCORE, %</td>
<td>23±18</td>
<td>22±18</td>
<td>18±14</td>
</tr>
<tr>
<td><strong>Medication</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta-blockers, n (%)</td>
<td>129(64)</td>
<td>81(64)</td>
<td>51(70)</td>
</tr>
<tr>
<td>ACEI/ARB, n (%)</td>
<td>117(58)</td>
<td>71(56)</td>
<td>42(58)</td>
</tr>
<tr>
<td>Statins, n (%)</td>
<td>127(63)</td>
<td>77(61)</td>
<td>42(58)</td>
</tr>
<tr>
<td>----------------</td>
<td>---------</td>
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</tbody>
</table>

**Doppler-echocardiographic Data**

**LV Dimensions and Systolic Function**

<table>
<thead>
<tr>
<th>LV end-diastolic diameter, mm</th>
<th>58±10</th>
<th>59±10</th>
<th>62±11</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV end-systolic diameter, mm</td>
<td>48±10</td>
<td>49±10</td>
<td>51±12</td>
</tr>
<tr>
<td>LV stroke volume, ml</td>
<td>57±17</td>
<td>59±19</td>
<td>64±20</td>
</tr>
<tr>
<td>LV stroke volume index, ml/m²</td>
<td>31±9</td>
<td>32±9</td>
<td>34±10</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>29±9</td>
<td>28±8</td>
<td>27±9</td>
</tr>
<tr>
<td>Global longitudinal strain, [%]</td>
<td>-</td>
<td>9.4±3.0</td>
<td>9.2±3.0</td>
</tr>
</tbody>
</table>

**Aortic Stenosis severity**

| Mean gradient, mmHg | 24±9 | 24±9 | 25±8 |
| Aortic valve area, cm² | 0.84±0.24 | 0.85±0.25 | 0.89±0.23 |
| Projected aortic valve area, cm² | 1.02±0.21 | 1.0±0.20 | 0.99±0.18 |

**Legend:** *: Subset of patients with coronary artery disease. **: Subset of patients with concomitant coronary artery bypass graft. NYHA: New York Heart Association; COPD: Chronic Obstructive Pulmonary Disease; ACEI: Angiotensin-Converting Enzyme Inhibitor; ARB: Angiotensin Receptor Blocker; LV: Left Ventricle. Values are mean ±SD unless otherwise indicated.
Table S2. Baseline Clinical and Doppler-echocardiographic Characteristics in the Subcohorts with and without Rest GLS Data Available

<table>
<thead>
<tr>
<th>Demographics and Physical Exam</th>
<th>Cohort with GLS available (n=126)</th>
<th>Cohort without GLS available (n=76)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>72±9</td>
<td>73±10</td>
<td>0.27</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>104(83)</td>
<td>53(70)</td>
<td>0.02</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>1.85±0.2</td>
<td>1.83±0.22</td>
<td>0.52</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>71±13</td>
<td>71±16</td>
<td>0.93</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>120±18</td>
<td>122±17</td>
<td>0.43</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>71±10</td>
<td>73±11</td>
<td>0.26</td>
</tr>
<tr>
<td>NYHA functional class ≥III, n (%)</td>
<td>61(48)</td>
<td>42(55)</td>
<td>0.33</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk factors and concomitant diseases</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension, n (%)</td>
<td>78(62)</td>
<td>49(64)</td>
<td>0.86</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>42(33)</td>
<td>29(39)</td>
<td>0.36</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>89(71)</td>
<td>54(71)</td>
<td>1.0</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>84(67)</td>
<td>38(50)</td>
<td>0.01</td>
</tr>
<tr>
<td>Coronary artery disease, n (%)</td>
<td>86(68)</td>
<td>54(71)</td>
<td>0.80</td>
</tr>
<tr>
<td>Multi-vessel coronary disease, n (%)</td>
<td>62(49)</td>
<td>43(56)</td>
<td>0.30</td>
</tr>
<tr>
<td>Number of diseased coronary vessels, n*</td>
<td>2.2±0.9</td>
<td>2.4±0.8</td>
<td>0.21</td>
</tr>
<tr>
<td>Previous coronary artery bypass graft, n (%)</td>
<td>34(27)</td>
<td>23(30)</td>
<td>0.65</td>
</tr>
<tr>
<td>Previous myocardial infarction, n (%)</td>
<td>70(56)</td>
<td>39(52)</td>
<td>0.45</td>
</tr>
<tr>
<td>Concomitant coronary artery bypass graft, n (%)</td>
<td>35 (28)</td>
<td>17(22)</td>
<td>0.34</td>
</tr>
<tr>
<td>Number of grafted coronary vessel, n**</td>
<td>2.0±1.1</td>
<td>2.4±1.3</td>
<td>0.26</td>
</tr>
<tr>
<td>COPD, n (%)</td>
<td>33(26)</td>
<td>23(30)</td>
<td>0.49</td>
</tr>
<tr>
<td>Logistic EuroSCORE, %</td>
<td>22±18</td>
<td>28±20</td>
<td>0.05</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medication</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-blockers, n (%)</td>
<td>81(64)</td>
<td>48(63)</td>
<td>0.90</td>
</tr>
<tr>
<td>ACEI/ARB, n (%)</td>
<td>71(56)</td>
<td>46(61)</td>
<td>0.55</td>
</tr>
</tbody>
</table>
Statins, n (%) 77(61) 50(66) 0.56

**Doppler-echocardiographic Data**

**LV Dimensions and Systolic Function**

<table>
<thead>
<tr>
<th></th>
<th>Statins</th>
<th>Control</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV end-diastolic diameter, mm</td>
<td>59±10</td>
<td>57±9</td>
<td>0.10</td>
</tr>
<tr>
<td>LV end-systolic diameter, mm</td>
<td>49±10</td>
<td>47±10</td>
<td>0.12</td>
</tr>
<tr>
<td>LV stroke volume, ml</td>
<td>59±19</td>
<td>55±15</td>
<td>0.15</td>
</tr>
<tr>
<td>LV stroke volume index, ml/m²</td>
<td>32±9</td>
<td>30±7</td>
<td>0.13</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>28±8</td>
<td>29±9</td>
<td>0.44</td>
</tr>
<tr>
<td>Global longitudinal strain,</td>
<td>9.4±3.0</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**Aortic Stenosis severity**

<table>
<thead>
<tr>
<th></th>
<th>Statins</th>
<th>Control</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean gradient, mmHg</td>
<td>24±9</td>
<td>23±8</td>
<td>0.33</td>
</tr>
<tr>
<td>Aortic valve area, cm²</td>
<td>0.85±0.25</td>
<td>0.83±0.23</td>
<td>0.88</td>
</tr>
<tr>
<td>Projected aortic valve area, cm²</td>
<td>1.0±0.20</td>
<td>1.03±0.22</td>
<td>0.76</td>
</tr>
</tbody>
</table>

**Legend:** The p value is for the comparison of Cohort with rest GLS available versus that with no rest GLS available. *: Subset of patients with coronary artery disease. **: Subset of patients with concomitant coronary artery bypass graft. NYHA: New York Heart Association; COPD: Chronic Obstructive Pulmonary Disease; ACEI: Angiotensin-Converting Enzyme Inhibitor; ARB: Angiotensin Receptor Blocker; LV: Left Ventricle. Values are mean ±SD unless otherwise indicated.
| Demographics and Physical Exam | Stress GLS>|10|% (n=38) | Stress GLS<|10|% (n=35) | P value |
|-------------------------------|-----------------|-----------------|---------|
| Age, years                    | 72±10           | 71±10           | 0.73    |
| Male gender, n (%)            | 29(76)          | 30(86)          | 0.30    |
| Body surface area, m<sup>2</sup> | 1.89±0.21     | 1.85±0.21       | 0.48    |
| Heart rate, bpm               | 69±13           | 74±14           | 0.09    |
| Systolic blood pressure, mmHg | 121±21          | 116±20          | 0.36    |
| Diastolic blood pressure, mmHg| 70±10           | 71±11           | 0.90    |
| NYHA functional class ≥III, n (%) | 9(24)         | 19(54)          | 0.007   |

| Risk factors and concomitant diseases | Stress GLS>|10|% (n=38) | Stress GLS<|10|% (n=35) | P value |
|--------------------------------------|-----------------|-----------------|---------|
| Hypertension, n (%)                  | 21(55)          | 21(60)          | 0.68    |
| Diabetes, n (%)                      | 15(39)          | 15(43)          | 0.76    |
| Dyslipidemia, n (%)                  | 23(61)          | 27(77)          | 0.13    |
| Smoking, n (%)                       | 25(66)          | 23(66)          | 1.0     |
| Coronary artery disease, n (%)       | 21(55)          | 25(71)          | 0.15    |
| Multi-vessel coronary disease, n (%) | 18(47)          | 18(51)          | 0.73    |
| Number of diseased coronary vessels, n* | 2.5±0.8       | 2.1±0.9         | 0.10    |
| Previous coronary artery bypass graft, n (%) | 11(29)       | 11(31)          | 0.82    |
| Previous myocardial infarction, n (%) | 19(50)         | 23(66)          | 0.17    |
| Concomitant coronary artery bypass graft, n (%) | 7(18)         | 5(14)           | 0.76    |
| Number of grafted coronary vessel, n** | 1.9±0.7        | 1.9±1.2         | 1.0     |
| COPD, n (%)                          | 11(29)          | 6(17)           | 0.06    |
| Logistic EuroSCORE, %               | 18±12           | 17±16           | 0.90    |

<p>| Medication | Stress GLS&gt;|10|% (n=38) | Stress GLS&lt;|10|% (n=35) | P value |
|------------|-----------------|-----------------|---------|
| Beta-blockers, n (%) | 26(68)          | 25(71)          | 0.77    |
| ACEI/ARB, n (%)        | 25(66)          | 17(49)          | 0.14    |</p>
<table>
<thead>
<tr>
<th></th>
<th>Statins, n (%)</th>
<th>Doppler-echocardiographic Data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>21(55)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>21(60)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.68</td>
<td></td>
</tr>
</tbody>
</table>

**Legend:** *: Subset of patients with coronary artery disease. **: Subset of patients with concomitant coronary artery bypass graft. NYHA: New York Heart Association; COPD: Chronic Obstructive Pulmonary Disease; ACEI: Angiotensin-Converting Enzyme Inhibitor; ARB: Angiotensin Receptor Blocker; LV: Left Ventricle. Values are mean ±SD unless otherwise indicated.

### LV Dimensions and Systolic Function

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Stress</th>
<th>p-value</th>
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<tbody>
<tr>
<td>LV end-diastolic diameter, mm</td>
<td>60±7</td>
<td>63±14</td>
<td>0.38</td>
</tr>
<tr>
<td>LV end-systolic diameter, mm</td>
<td>48±9</td>
<td>54±13</td>
<td>0.09</td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Stress</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV stroke volume, ml</td>
<td>69±16</td>
<td>58±23</td>
<td>0.019</td>
</tr>
<tr>
<td>LV stroke volume index, ml/m²</td>
<td>38±7</td>
<td>31±12</td>
<td>0.005</td>
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<table>
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<th>Rest</th>
<th>Stress</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV ejection fraction, %</td>
<td>32±6</td>
<td>23±8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Global longitudinal strain, [%]</td>
<td>10.8±2.4</td>
<td>7.4±2.6</td>
<td>&lt;0.0001</td>
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</tbody>
</table>

**Aortic Stenosis severity**

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Stress</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean gradient, mmHg</td>
<td>26±8</td>
<td>24±8</td>
<td>0.24</td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Stress</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic valve area, cm²</td>
<td>0.91±0.20</td>
<td>0.87±0.24</td>
<td>0.45</td>
</tr>
<tr>
<td>Projected aortic valve area, cm²</td>
<td>0.97±0.17</td>
<td>1.00±0.18</td>
<td>0.38</td>
</tr>
</tbody>
</table>
FIGURE S1. Relative Risk of All-Cause Mortality as a Function of Global Longitudinal Strain

Caption: Curves of mean (black) and 95% confidence interval (grey) of the relative risk ratio for rest (Panel A) and stress (Panel B) global longitudinal strain. The intersection of the mean relative risk curve with the 1.0 value (dashed line) is at 9.38 % for rest GLS and 10.18 % for stress GLS.
Panel B

The graph shows the relationship between Stress Global Longitudinal Strain, (%) and Relative Risk of Mortality. The x-axis represents Stress Global Longitudinal Strain, (%) ranging from 3 to 21, while the y-axis represents Relative Risk of Mortality ranging from 0.1 to 4.0. Several curves are plotted, with one main black curve and two light gray curves, indicating different levels of risk.
FIGURE S2. Correlation between Rest and Stress Global Longitudinal Strain.

Caption: GLS: global longitudinal strain.
FIGURE S3. Correlation between LV ejection fraction and Global Longitudinal Strain at Rest (Panel A) and During Dobutamine Stress Echocardiography (Panel B).

Caption: GLS: global longitudinal strain; LVEF: LV ejection fraction
Panel B

Stress LVEF (%) vs. Stress GLS (|%|)

$r=0.72$
$p<0.0001$
FIGURE S4. Incremental Prognostic Value of Rest Global Longitudinal Strain Beyond LV Ejection and Other Risk Factors

Caption: This figure shows the Chi$^2$ of the multivariable model including baseline (BSL) risk factors (i.e. age, coronary artery disease, AVAproj, and type of treatment), LV ejection fraction (LVEF) and/or global longitudinal strain (GLS). Panel A shows the incremental prognostic value of rest GLS and Panel B shows the incremental value of stress GLS.

Panel A