

Outcomes in Asymptomatic Severe Aortic Stenosis With Preserved Ejection Fraction Undergoing Rest and Treadmill Stress Echocardiography

Chetan P. Huded, MD, MSc;* Ahmad Masri, MD;* Kenya Kusunose, MD, PhD; Andrew L. Goodman, MD; Richard A. Grimm, DO; A. Marc Gillinov, MD; Douglas R. Johnston, MD; L. Leonardo Rodriguez, MD; Zoran B. Popovic, MD, PhD; Lars G. Svensson, MD, PhD; Brian P. Griffin, MD; Milind Y. Desai, MD

Background—In asymptomatic patients with severe aortic stenosis and preserved left ventricular ejection fraction, we sought to assess the incremental prognostic value of resting valvuloarterial impedance (Zva) and left ventricular global longitudinal strain (LV-GLS) to treadmill stress echocardiography.

Methods and Results—We studied 504 such patients (66 ± 12 years, 78% men, 32% with coronary artery disease who underwent treadmill stress echocardiography between 2001 and 2012. Clinical and exercise variables (% of age-sex predicted metabolic equivalents [%AGP-METs]) were recorded. Resting Zva ([systolic arterial pressure+mean aortic valve gradient]/[LV-stroke volume index]) and LV-GLS (measured offline using Velocity Vector Imaging, Siemens) were obtained from the baseline resting echocardiogram. Death was the primary outcome. There were no major adverse cardiac events during treadmill stress echocardiography. Indexed aortic valve area, Zva, and LV-GLS were 0.46 ± 0.1 cm²/m², 4.5 ± 0.9 mm Hg/mL per m² and $-16 \pm 4\%$, respectively; only 50% achieved >100% AGP-METs. Sixty-four percent underwent aortic valve replacement. Death occurred in 164 (33%) patients over 8.9 ± 3.6 years (2 within 30 days of aortic valve replacement). On multivariable Cox survival analysis, higher Society of Thoracic Surgeons score (hazard ratio or HR 1.06), lower % AGP-METS (HR 1.16), higher Zva (HR 1.25) and lower LV-GLS (HR 1.12) were associated with higher longer-term mortality, while aortic valve replacement (HR 0.45) was associated with improved survival (all $P < 0.01$). Sequential addition of Zva and LV-GLS to clinical model (Society of Thoracic Surgeons score and %AGP-METs) increased the c-statistic from 0.65 to 0.69 and 0.75, respectively, both $P < 0.001$); findings were similar in the subgroup of patients who underwent aortic valve replacement.

Conclusions—In asymptomatic patients with severe aortic stenosis undergoing treadmill stress echocardiography, LV-GLS and Zva offer incremental prognostic value. (*J Am Heart Assoc.* 2018;7:e007880. DOI: 10.1161/JAHA.117.007880.)

Key Words: aortic stenosis • strain • stress echocardiography

Aortic valve replacement (AVR) is a Class I indication in asymptomatic severe aortic stenosis (AS) and leads to a significant improvement in survival.^{1,2} However, the management of asymptomatic patients with severe AS remains

controversial and as AVR techniques become safer and less morbid, the threshold for valve replacement is becoming less stringent. Although the risk of sudden death in asymptomatic patients with severe AS is low (<1%/year), once symptomatic 3% of patients may die within 6 months, with an overall mortality of 50% over 2 years.^{3–6} The decision about timing of AVR in patients with significant AS requires a careful assessment of the risk–benefit ratio of AVR versus watchful waiting. However, the patients' perception of their symptoms is often misleading; and patients may be more symptomatic than they realize as they may have unknowingly adjusted their exercise to meet the reduced capability. When symptom status is a concern, stress testing can provide objective insight into functional capacity and hemodynamic responses.

Previous studies have demonstrated the safety of stress testing in carefully selected asymptomatic patients with severe AS.^{7,8} According to guidelines, AVR is recommended for symptomatic patients with severe high-gradient AS who

From the Heart Valve Center, Heart and Vascular Institute, Cleveland Clinic, Cleveland, OH.

Accompanying Data S1, Tables S1, S2, and Figures S1, S2 are available at <http://jaha.ahajournals.org/content/7/8/e007880/DC1/embed/inline-supplementary-material-1.pdf>

*Dr Huded and Dr Masri are co-first authors and contributed equally to this work.

Correspondence to: Milind Desai, MD, Heart and Vascular Institute, Cleveland Clinic, 9500 Euclid Ave, Desk J1-5, Cleveland, OH 44195. E-mail: desaim2@ccf.org

Received October 16, 2017; accepted February 27, 2018.

© 2018 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

Clinical Perspective

What is New?

- In asymptomatic patients with severe aortic stenosis undergoing rest and exercise echocardiography, we demonstrate valvuloarterial impedance and left ventricular global longitudinal strain provide synergistic and incremental prognostic value in addition to exercise capacity.

What Are the Clinical Implications?

- While the role of aortic valve replacement is generally well-accepted in symptomatic patients with severe aortic stenosis, our findings suggest that careful attention to sensitive markers such as valvuloarterial impedance and left ventricular global longitudinal strain, along with an evaluation of exercise capacity, may potentially identify higher risk patients with apparently asymptomatic severe aortic stenosis, thus aiding in optimal timing of aortic valve replacement.

have symptoms on exercise testing (Class Ib). In addition, exercise-induced drop in systolic blood pressure is a Class IIa indication for surgery.^{1,2} However, these recommendations are based upon multiple small reports with heterogeneous end points.^{3,9–15} In a recent study, we have demonstrated that in asymptomatic patients with severe AS and preserved left ventricular ejection fraction (LVEF), only 50% achieved 100% of age-sex predicted exercise capacity; with exercise stress testing providing significant reclassification of longer-term mortality risk.¹⁶ In the past decade, novel echo parameters including reduced left ventricular global longitudinal strain (LV-GLS)^{17–19} and valvuloarterial impedance (Zva)^{17,19,20} have also been associated with worse prognosis in patients with asymptomatic severe AS. However, no study has systematically evaluated the incremental prognostic impact of resting Zva and LV-GLS on data obtained from exercise stress testing in patients with asymptomatic severe AS and preserved LVEF. Therefore, we sought to assess whether resting Zva and LV-GLS provide synergistic and incremental prognostic utility to clinical and treadmill echocardiographic variables in a large contemporary cohort of asymptomatic patients with severe AS and preserved LVEF.

Methods

Study Design

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. This was a retrospective observational study of 504 consecutive patients with severe AS (indexed valve area $0.6 \text{ cm}^2/\text{m}^2$ on resting

echocardiogram) and preserved LVEF $\geq 50\%$ who underwent treadmill stress echocardiography (TSE) at our center between January 2001 and December 2012.¹⁶ Figure 1 demonstrates the flow diagram of final patient selection. According to our institutional policy on severe AS, only those who are deemed asymptomatic and free of co-morbidities (that would preclude exercising on a treadmill), after a thorough clinical evaluation undergo treadmill stress testing. No patient a) had critical AS (mean AV gradient $\geq 50 \text{ mm Hg}$, as it is an indication for surgery) or b) underwent balloon aortic valvuloplasty or transcatheter AVR (as it was not offered in low-risk individuals with severe AS). The primary indications for the stress test were to elicit symptoms (and confirm true asymptomatic status), assess functional capacity and blood pressure/ischemic LV response. Society of Thoracic Surgeons (STS) score and Charlson comorbidity index (as a surrogate for frailty)²¹ were calculated. Data were prospectively entered at the time of initial encounter and manually extracted for the study, after appropriate Institutional Review Board approval with waiver of individual informed consent.

Rest and Stress Echocardiographic Data

All patients underwent a comprehensive transthoracic echocardiogram with commercially available instruments (Philips Medical Systems, NA, Bothell, WA; General Electric Medical Systems, Milwaukee, WI; and Siemens Medical Solutions USA, Inc, Malvern, PA) as part of a standard clinical diagnostic evaluation. LV measurements (indexed to body surface area or BSA), including ejection fraction (by 2D biplane), mass and diastolic function were obtained according to guidelines.^{22–24} We used a semiquantitative 5-point scale (non-severe) to stratify valvular regurgitation, along with right ventricular systolic pressure (RVSP).²⁵ Quantitative parameters related to AS were measured, as described.²⁶ LV outflow tract (LVOT) diameter was measured on parasternal long-axis views. Pulsed-wave and continuous-wave Doppler were used to record peak velocities and gradients across the LVOT and aortic valve (AV), respectively, in different views. AV area (AVA) was calculated using the continuity equation and subsequently indexed to BSA. LV stroke volume index (LV-SVI) was measured using the following formula: $\text{LVOT}_{\text{VTI}} \times \text{LVOT}_{\text{area}}/\text{BSA}$. A cutoff $\geq 35 \text{ mL}/\text{m}^2$ was considered as preserved LV-SVI.^{27–29} Additionally, Zva was measured using the following formula: $(\text{systolic arterial pressure, measured at the time of echocardiography} + \text{mean aortic valve pressure gradient})/\text{LV-SVI}$.^{19,21,22}

LV-GLS measurements were obtained from baseline transthoracic echocardiographic gray-scale images of apical 2, 3, and 4 chamber views. The frame rate was >30 frames per second. LV-GLS was analyzed offline using Velocity Vector

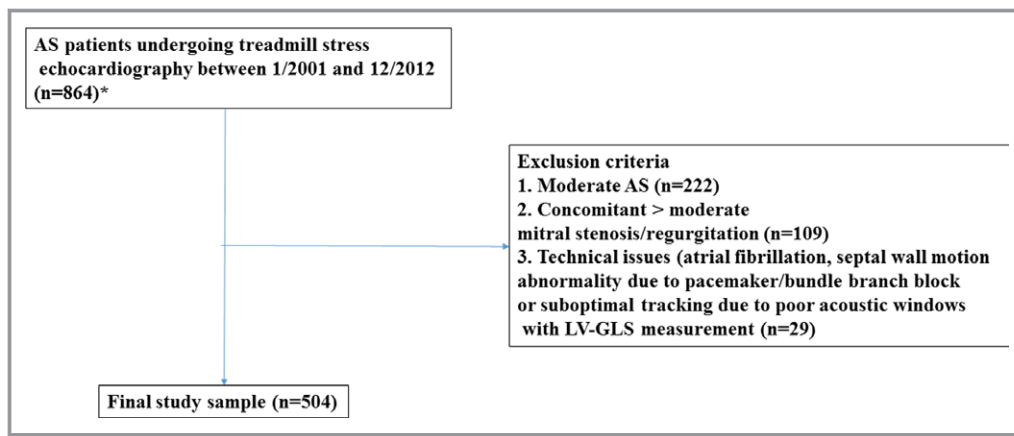


Figure 1. Flow diagram of patient selection. AS=aortic stenosis, LV-GLS=left ventricular global longitudinal strain.

Imaging (Syngo VVI, Siemens Medical Solutions, Mountain View, CA) as previously described.³⁰ After manual definition of LV endocardium, it was automatically tracked throughout the cardiac cycle. LV-GLS was obtained by averaging all segmental strain values and by averaging all 3 apical views. Peak global strain was defined as peak negative value on the strain curve during the entire cardiac cycle. Since reported LV-GLS values are negative, a lower absolute number represented a worse value than higher. Inter and intra-observer reproducibility of LV-GLS in AS patients has been described previously by the current group of investigators.³⁰

Subsequently, patients underwent TSE, as previously described.¹⁶ Standard measurements were made at rest, at 1 minute intervals and for ≥ 6 minutes in recovery. Maximal predicted heart rate ($220 - \text{age}$), %-predicted maximal heart rate, heart rate recovery (HRR, drop in heart rate from peak to 1 minute post exercise)³¹ and number of metabolic equivalents (METs) achieved were recorded. To calculate the expected METs based on age and sex, we used Veterans Affairs cohort formula in men ($\text{predicted METs} = 18 - [0.15 \times \text{age}]$)³² and St. James Take Heart Project formula ($\text{predicted METs} = 14.7 - [0.13 \times \text{age}]$) in women,³³ as they have been previously demonstrated to best predict outcomes in respective sexes.³⁴ We subsequently calculated % age-sex predicted METs (AGP-METs) as the following ratio: $(\text{METs achieved} / \text{age-sex expected METs}) \times 100$. Chronotropic Response Index (CRI), was calculated using the following formula: $(\text{Peak HR} - \text{Resting HR}) / (220 - \text{Age} - \text{Resting HR})$.³⁵ Duke treadmill score was calculated.³⁶

Immediately following exercise, peak-stress echocardiographic images were acquired, according to guidelines,³⁷ and the following parameters were assessed: regional wall motion abnormalities for evaluation of ischemia and peak RVSP. Post-stress AV gradients were recorded, where available. We acquired all data from the standard windows (parasternal and apical). However, when the resting suprasternal gradients

were much higher than apical gradients, suprasternal gradients were also recorded, after all standard views were obtained. Major (death, sustained ventricular or atrial arrhythmias associated with severe symptoms, hemodynamic compromise, or need for cardioversion) and minor complications (decrease in blood pressure, transient symptoms, or nonsustained arrhythmias) were recorded.

Surgical Details

Cardiac surgical procedures were categorized as follows: (1) isolated AVR, (2) AVR and coronary artery bypass grafting (CABG) and (3) AVR and ascending aorta repair or replacement \pm CABG. Time to surgery was recorded. The primary indications for surgery included a) abnormalities on stress testing (abnormal blood pressure/ischemic LV response to stress and symptomatic functional capacity impairment) or development of symptoms during follow-up. The primary reasons to not operate were as follows: no stress abnormalities (normal BP response and no ischemia) and lack of symptoms at stress testing. In addition, these non-operated patients were evaluated periodically at our institution to confirm lack of symptom development. There were no patients who had non-cardiac co-morbidities precluding referral to AVR. Decision to undergo AVR was made by the evaluating cardiologist and cardiothoracic surgeon.

Outcomes Analysis

All-cause mortality was the primary outcome. Death was confirmed by querying nationally available databases, inspection of the death certificate or verified with a family member. In addition, we further identified patients with a non-cardiac (e.g., malignancy, cirrhosis, primary pulmonary/neurologic etiology) etiology of death. The duration of follow-up ranged from the initial stress echocardiogram to December 2016.

Statistical Analysis

Continuous variables are expressed as mean±standard deviation and/or median with interquartile range and compared using analysis of covariance (for normally distributed variables) or Mann–Whitney test (for non-normally distributed variables). Categorical data is expressed as percentage and compared using chi-square. To assess outcomes, Cox proportional hazards analysis was performed. For multivariable analysis, we created a parsimonious model in which pre-specified variables, known to be associated with adverse outcomes in AS patients, were considered. Even though STS score was developed to predict 30-day/in-hospital perioperative mortality, we chose to include STS score in longer-term survival analyses as it represents a composite of various predictors that are known to be associated with outcomes in AS patients.²⁶ In the initial multivariable Cox proportional hazards analysis of the entire study sample, AVR was included as a time-dependent covariate in Cox survival analysis (because of significant time between stress test and AVR). For each patient undergoing AVR, the analysis time was modeled so that only the person-time after AVR was included in surgical group. We also performed multivariable Cox survival analysis in the subgroup that underwent AVR during follow-up. Hazard ratios (HR) with 95% confidence intervals were calculated. For secondary outcomes analysis, since longer-term cardiac and non-cardiac deaths were competing risks, multivariable survival analysis was performed by competing risk regression analysis using the Fine-Gray proportional subhazards model, and subdistribution hazard ratios (sHR) were calculated, along with 95% confidence intervals.³⁸ Cumulative proportion of patients with events as a function over time was obtained by Kaplan–Meier method and compared using log-rank test. Kaplan–Meier analysis was also performed in various subgroups (based on [1] achieving ≥85% AGP-METs and subsequent AVR versus no AVR, [2] median LV-GLS and achievement of 85% AGP-METs, [3] median Zva and achievement of 85% AGP-METs and [4] based on median Zva and LV-GLS). We also assessed the reclassification of longer-term mortality risk using net reclassification improvement (NRI). Discriminative ability of various survival models were compared using the c-statistic. Similar to above, for each patient undergoing AVR, the analysis time was modeled so that only the person-time after AVR was included in surgical group. The functional relationship between Zva, LV-GLS and risk of death was assessed using a parametric multiphase hazard model.³⁹ The best fitting model was obtained when Zva and LV-GLS were modeled using quadratic splines with 5 knots at 10th, 25rd, 50th, 75th, and 90th percentile values of Zva and LV-GLS. To evaluate the relationship between Zva, LV-GLS and risk of death by AV surgery (versus not), the variable for AV surgery was entered into this model. Similarly, to evaluate the

relationship between Zva, LV-GLS, and risk of death by AGP-METs (higher or lower than 85%), the variable for AGP-METs was entered into this model. Nomograms were used to depict the estimated survival or corresponding hazard rate at specified time points for the overall cohort and for the cohort stratified by surgical versus non-surgical and low versus normal AGP-METs. Statistical analysis was performed using SPSS version 11.5 (SPSS Inc., Chicago, IL), SAS version 9.4 (Cary, NC) and R 3.0.3 (R foundation for Statistical Computing, Vienna, Austria). A $P<0.05$ was considered significant.

Results

Despite being asymptomatic, only 252 (50%) patients achieved >100% AGP-METs, while 123 (24%) achieved between 85% and 100% and 129 (26%) achieved <85% AGP-METs. There were no deaths, syncope, significant atrial/ventricular arrhythmias or acute coronary syndromes precipitated by the stress test. Five patients (1%) had nonsustained ventricular tachycardia during stress that spontaneously resolved. Baseline characteristics are shown in Tables 1 and 2. Median LV-GLS and Zva were -15.8 (-19.8 , -12.6) and 4.5 mm Hg/mL per m^2 (3.9 , 5.1), respectively. Relevant characteristics, separated based on median LV-GLS and Zva are shown in Tables S1 and S2. There was weak but significant association between % AGP-METs and LV-GLS (beta= -0.22 , standard error 0.007, $P<0.001$) and Zva (beta= -0.18 , standard error 0.001, $P<0.001$), respectively. In addition, there was a weak but significant association between LV-GLS and Zva (beta= 0.21 , standard error 0.01, $P<0.001$). Mean aortic valve (AV) gradient at peak-stress was 44 ± 12 mm Hg (data available in only 281 patients). Of these, only 48 (17%) patients had an abnormal increase (≥ 20 mm Hg) in mean AV gradient at peak-stress.^{11,40}

During follow-up, 323 (64%) patients underwent surgery as follows: 175 (54%) isolated AVR, 114 (35%) AVR+CABG and 34 (10%) AVR+aortic replacement ±CABG. The primary indications for surgery included (1) abnormal blood pressure/LV response on stress echocardiography ($n=25$, 8%) (2) symptomatic functional capacity impairment, $n=117$, 36%) or development of overt symptoms during follow-up ($n=156$, 56%). The median interval between stress test and AVR was 159 (23, 597) days (patients with abnormal stress test ($n=142$) underwent surgery within 60 days). There were no deaths between stress test and AVR in patients who were considered for surgery.

Of the 181 patients who did not undergo surgery, none had symptoms or abnormal blood pressure/ischemia during stress and were perceived to be asymptomatic during follow-up, with the vast majority ($n=126$ or 70%) achieving $\geq 85\%$ AGP-METs (mean METs 8.6 ± 3). There were 55 (30%) remaining patients who achieved <85% AGP-METs (mean

Table 1. Clinical and Demographic Characteristics of the Study Sample (N=504)

Variable	Total Population (N=504)	Age-Sex Predicted METS <85% (n=129)	Age-Sex Predicted METS ≥85% (n=375)	P Value
Age, y	66±12	65±12	66±12	0.21
Male sex	392 (78%)	99 (77%)	293 (78%)	0.42
Body mass index, kg/m ²	28±5	28±5	28±5	0.51
Hypertension	358 (70%)	91 (72%)	267 (72%)	0.97
Hyperlipidemia	351 (70%)	259 (69%)	92 (71%)	0.36
Diabetes mellitus	84 (16%)	24 (19%)	60 (16%)	0.42
Prior stroke	27 (5%)	80 (6%)	19 (5%)	0.38
Smoking history	247 (49%)	65 (50%)	182 (49%)	0.72
Obstructive CAD	160 (32%)	42 (33%)	118 (32%)	0.47
Prior cardiac surgery	89 (18%)	28 (16%)	61 (16%)	0.11
STS score	2.88±3	2.64±3	2.97±3	0.33
Charlson co-morbidity index	2.68±1.5	2.78±1.6	2.64±1.5	0.36
Betablockers	200 (41%)	61 (49%)	139 (38%)	0.08
ACE-inhibitors	177 (36%)	44 (36%)	133 (36%)	0.71
Aspirin	295 (59%)	74 (57%)	221 (59%)	0.76
Statins	278 (56%)	68 (55%)	210 (57%)	0.20
Glomerular filtration rate (mL/min per 1.73 m ²)	88±32	87±32	90±38	0.36

P-values reflect comparison between subgroups. ACE indicates angiotensin converting enzyme; CAD, coronary artery disease; METs, metabolic equivalents; STS, Society of thoracic surgeons.

METS 6.9±2) but did not undergo surgery at the discretion of the evaluating cardiologist, primarily because of perceived lack of symptoms at the time of evaluation and subsequent follow-up. There were no patients who had non-cardiac co-morbidities precluding referral to AVR. No patient had follow-up stress echocardiography.

Outcomes

During a mean follow up of 8.9±3.6 years (median 8.7 years [6.7, 11.5]), 164 (33%) patients died. Of these, 16 (10%) had a documented non-cardiac death. Only 2 patients died within 30-days following AVR; and at 1-year, there were an additional 8 deaths. The data on multivariable Cox Proportional Hazard analysis for longer-term all-cause mortality in the entire study sample are shown in Table 3. Higher STS score (HR 1.06), lower % AGP-METS (HR 1.16), slower HRR (HR 1.18), lower LV-GLS (HR 1.12) and higher Zva (HR 1.25) were associated with higher longer-term mortality, while AVR (time dependent covariate, HR 0.45) was associated with improved survival. The findings were similar in the subgroup that underwent AVR (n=323, number of deaths=84) during follow-up. Neither quadratic nor cubic transformations of STS score, LV-GLS, or Zva were significant predictors of mortality when forced into Cox model that already included these variables in a non-

transformed form. Table 4 demonstrates the incremental prognostic utility (c-statistic and NRI) of various predictors in the entire study sample (STS score, %AGP-METS, Zva, LV-GLS and AVR) as well as in the subgroup that underwent AVR during follow-up (STS score, % AGP-METS, Zva and LV-GLS).

The proportion of long-term deaths in the subgroup achieving <85% AGP-METS was significantly higher versus those achieving ≥85% (63 [49%] versus 101 [27%], log-rank statistic 27, *P*<0.001). A significantly lower proportion of patients who underwent AVR versus those who did not died (84 [26%] versus 80 [44%], log-rank statistic 41, *P*<0.001). Also, the proportion of long-term deaths in those with LV-GLS worse than median was significantly higher versus those whose LV-GLS was better than median (114 [45%] versus 50 [20%], log-rank statistic 45, *P*<0.001). The Kaplan–Meier curves of the study sample, separated based on median LV-GLS are shown in Figure 2A. Similarly, the proportion of long-term deaths in those with Zva worse (higher) than median was significantly higher versus those whose Zva was better (lower) than median (103 [41%] versus 61 [24%], log-rank statistic 11, *P*<0.001). The Kaplan–Meier curves of the study sample, separated based on median Zva, are shown in Figure 2B.

The proportion of deaths in 4 subgroups, based on median LV-GLS and 85% AGP-METS, were significantly different (log-rank 79, *P*<0.001), as follows: (1) ≥85% AGP-METS, LV-GLS

Table 2. Rest and Post-Exercise Echocardiographic Data in the Study Sample (N=504)

Variable	Total Population (N=504)	Age-Sex Predicted METs <85% (n=129)	Age-Sex Predicted METs ≥85% (n=375)	P Value
Resting echocardiography				
LV ejection fraction, %	58±4	57±5	58±4	0.12
Indexed LVESD, cm/m ²	1.4±0.3	1.4±0.3	1.4±0.3	0.75
Indexed LV mass, g/m ²	116±36	115±35	116±39	0.87
Indexed left atrial dimension, cm/m ²	2.0±0.4	2.0±0.4	2.0±0.4	0.72
Diastolic dysfunction				
Abnormal relaxation	459 (91%)	114 (88%)	345 (92%)	0.49
Pseudonormal	43 (9%)	14 (11%)	29 (8%)	
Restrictive filling	2 (0.4%)	1 (1%)	1 (0.2%)	
Bicuspid aortic valve	123 (25%)	30 (23%)	93 (25%)	0.72
Peak gradient, mm Hg	58±18	59±18	58±18	0.48
Mean AV gradient, mm Hg	35±11	36±12	35±12	0.51
AV area (cm ² , continuity)	0.79±0.2	0.77±0.2	0.79±0.2	0.34
Indexed AV area (cm ² /m ² , continuity)	0.46±0.1	0.45±0.1	0.46±0.1	0.12
Stroke volume index, mL/m ²	40±9	39±9	42±9	0.01
Zva	4.51±0.9	4.75±1.0	4.43±0.9	0.001
Zva worse than median	253 (50%)	76 (59%)	177 (47%)	
Zva better than median	251 (50%)	53 (41%)	198 (53%)	0.01
LV-GLS, %	-16.1±4	-15.1±4	-16.4±4	0.001
LV-GLS worse than median	251 (50%)	77 (60%)	174 (46%)	
LV-GLS better than median	253 (50%)	52 (40%)	201 (54%)	0.006
≥Moderate aortic regurgitation	104 (21%)	23 (18%)	81 (22%)	0.36
Resting RVSP, mm Hg	33±10	32±9	32±10	0.31
Exercise echocardiography				
Resting systolic blood pressure, mm Hg	137±18	137±18	137±20	0.67
Resting heart rate, bpm	68±13	68±13	68±13	0.59
Peak rate pressure product	22 911±5533	20 627±5476	23 690±5340	<0.001
Peak systolic blood pressure, mm Hg	165±27	156±32	168±25	<0.001
Peak heart rate, bpm	136±23	128±23	138±23	<0.001
% maximum predicted heart rate	88±13	90±12	84±13	<0.001
Chronotropic response index	0.79±0.2	0.67±0.2	0.83±0.2	<0.001
Maximum METs	7.7±3	5.4±2	8.5±2	0.007
Total exercise time, s	448±157	311±114	498±135	<0.001
Heart rate recovery, bpm	25±12	21±11	27±11	0.01
Symptoms at peak stress				
General fatigue	411 (82%)	93 (72%)	318 (85%)	0.01
Dyspnea	42 (8%)	15 (12%)	27 (7%)	
Angina	15 (3%)	4 (3%)	11 (3%)	
Abnormal BP response	25 (5%)	11 (9%)	14 (4%)	
Dizziness	3 (0.6%)	1 (0.8%)	2 (0.5%)	
Arrhythmias	8 (2%)	5 (4%)	3 (1%)	

Continued

Table 2. Continued

Variable	Total Population (N=504)	Age-Sex Predicted METS <85% (n=129)	Age-Sex Predicted METS ≥85% (n=375)	P Value
Duke treadmill score				
>5	261 (52%)	60 (47%)	201 (54%)	0.02
Between –10 and 5	163 (33%)	40 (31%)	123 (33%)	
<–10	11 (2%)	4 (3%)	7 (2%)	
Uninterpretable	69 (14%)	25 (19%)	44 (12%)	
Number of ischemic LV territories				
None	446 (89%)	112 (87%)	334 (89%)	0.74
1	47 (9%)	13 (10%)	34 (9%)	
2	7 (2%)	3 (2%)	4 (1%)	
3	4 (0.8%)	1 (0.8%)	3 (0.8%)	
Post-stress RVSP	48±19	49±20	48±21	0.39

P-values reflect comparison between subgroups. AV indicates aortic valve; BP, blood pressure; ESD, end-systolic dimension; LV, left ventricle; LV-GLS, left ventricular global longitudinal strain; METs, metabolic equivalents; RVSP, right ventricular systolic pressure; Zva, valvuloarterial impedence.

better than median (34/201 [17%]) (2) ≥85% AGP-METs, LV-GLS worse than median (67/174 [39%]) (3) <85% AGP-METs, LV-GLS better than median (16/52 [31%]) and (4) <85% AGP-METs, LV-GLS worse than median (47/67 [61%]). The Kaplan–Meier curves are shown in Figure 3A. Similarly, the proportion of deaths in the subgroups, based on median Zva and 85% AGP-METs, were significantly different (log-rank statistic 35, $P<0.001$), as follows: (1) ≥85% AGP-METs, Zva better than median (37/198 [19%]) (2) ≥85% AGP-METs, Zva worse than median (64/177 [36%]) (3) <85% AGP-METs, Zva better than median (24/53 [45%]) and (4) <85% AGP-METs, Zva worse than median (39/76 [51%]). The Kaplan–Meier curves are shown in Figure 3B. Additional subgroup Kaplan–Meier analyses are shown in Data S1 and Figure S1A and S1B.

For LV-GLS, the data on 5-year hazard (for death) using quadratic spline with 5 knots, for the study population as a whole as well as separated into AV surgery versus not, are shown in Figures 4A and 4B. In the entire cohort, patients with LV-GLS better than $\approx -17\%$ had excellent 5-year event-free survival; with a continuously increasing risk of death when LV-GLS was impaired below -17% (Figure 4A). However, when the cohort was separated based on AV surgery versus not, the risk of death continuously increased when LV-GLS was impaired below $\approx -22\%$ in the non-surgical group versus $\approx -12\%$ in the surgical group (Figure 4B). Similarly, for Zva, the data on 5-year hazard (for death) using quadratic spline with 5 knots, for the study population as a whole as well as separated into AV surgery versus not, are shown in Figures 5A and 5B. In the entire cohort, patients with Zva lower than ≈ 4.5 mm Hg/mL per m^2 had excellent 5-year event-free survival; with a continuously increasing risk of

death when Zva increased above 4.5 mm Hg/mL per m^2 (Figure 5A). However, when the cohort was separated based on AV surgery versus not, the risk of death continuously increased when Zva increased beyond 4 mm Hg/mL per m^2 in the non-surgical group versus ≈ 6 mm Hg/mL per m^2 in the surgical group (Figure 5B). Similar data on quadratic spline analyses for LV-GLS and Zva, separated into subgroups based on achieved AGP-METs higher or lower than 85% are shown in Figures S2A and S2B.

Additional survival analyses related to stratification based on a) presence or absence of documented obstructive coronary artery disease and b) documented cardiac versus non-cardiac deaths, were similar and are also shown in Data S1.

Discussion

In the current study of asymptomatic patients with severe AS and preserved LVEF undergoing TSE, we demonstrate that impaired LV-GLS and higher Zva were associated with increased longer-term mortality, while AVR was associated with improved longer-term survival. Addition of LV-GLS and Zva to exercise capacity incrementally and synergistically improved reclassification of longer-term mortality risk, including in the subgroup that underwent AVR. Performing AVR in the subgroup of patients with preserved LV-GLS and Zva (both better than median) was associated with the best longer-term survival as opposed to those in whom either LV-GLS or Zva were worse than median, suggesting that waiting for even subtle LV dysfunction might result in development of impaired subclinical LV function, which can potentially be associated with long-term mortality. We also demonstrate that while an

Table 3. Multivariable Cox Proportional Hazard Survival Analyses for Longer-Term All-Cause Mortality

Variable	Hazard Ratio	P Value
(A) Entire study sample (N=504)		
STS Score (for every 1% increase)	1.06 (1.02–1.10)	<0.001
% Age-sex predicted METs achieved (for every 10% decrease)	1.16 (1.09–1.23)	0.001
Heart rate recovery (for every 10 bpm slower recovery)	1.18 (1.05–1.39)	0.001
LV-GLS (for every 0.1% absolute impairment)	1.12 (1.07–1.16)	<0.001
Zva (for every 0.1 absolute value impairment)	1.25 (1.06–1.46)	0.001
Aortic valve surgery (time dependent covariate analysis)	0.45 (0.32–0.64)	<0.001
The following additional predictors were considered for analysis: Peak rate-pressure product, indexed LV mass, peak aortic valve gradient, ≥moderate resting aortic regurgitation, ischemic LV response to stress, resting right ventricular systolic pressure, time to aortic valve surgery. Interaction term between Zva and LV-GLS, when entered into the model was not significant.		
(B) Subgroup that underwent aortic valve replacement in follow-up (n=323)		
STS score (for every 1% increase)	1.12 (1.05–1.18)	<0.001
% Age-sex predicted METs achieved (for every 10% decrease)	1.10 (1.05–1.27)	<0.001
Heart rate recovery (for every 10 bpm slower recovery)	1.13 (1.03–1.42)	0.01
LV-GLS (for every 0.1% absolute impairment)	1.10 (1.04–1.17)	<0.001
Zva (for every 0.1 absolute value impairment)	1.19 (1.03–1.52)	0.001
The following additional predictors were considered for analysis: peak aortic valve gradient, ≥moderate resting aortic regurgitation, ischemic LV response to stress, resting right ventricular systolic pressure. Interaction term between Zva and LV-GLS, when entered into the model was not significant.		

Because not all patients had peak-stress mean aortic valve gradients measured, the variable of increase in aortic valve gradient between stress and rest was not included in the final multivariable model. Because STS score was entered in multivariable analysis, its individual predictors (like age, sex, LV ejection fraction, etc.) were not entered. Because of collinearity, only % age-sex predicted METs achieved (and not absolute METs or chronotropic response index), Zva (and not aortic valve gradient or stroke volume index), resting RVSP (and not post-exercise RVSP) and STS score (and not Charlson comorbidity index) were entered into the model. Results were similar if these variables were substituted in the models. LV-GLS indicates left ventricular global longitudinal strain; METs, metabolic equivalents; STS, Society of thoracic surgeons; Zva, valvuloarterial impedance.

LV-GLS cutoff worse than $\approx 17\%$ was associated with an increased risk of death in the whole cohort, the cutoffs were different in non-operated versus operated patients ($\approx -22\%$ versus -12% , respectively). Similarly, while a Zva cutoff higher than and $4.5 \text{ mm Hg/mL per m}^2$ was associated with an increased risk of death in the whole cohort, the cutoffs were different in non-operated versus operated patients (4 versus $6 \text{ mm Hg/mL per m}^2$, respectively). This likely suggests that the cutoffs of LV-GLS and Zva beyond which risk of death increases is positively modulated by AVR. Similar observations were made when the cohort was divided into subgroups achieving higher (or lower) than 85% AGP-METs.

The optimal management of patients with asymptomatic severe AS remains an area of considerable debate, and many studies have examined the issue of risk stratifying these patients to identify patients who should be referred for early AVR before symptom onset.^{41,42} However, no prior report has demonstrated the synergistic value of novel and sensitive echocardiographic markers to the risk-prediction algorithm based on a combination of rest and exercise echocardiography, particularly in asymptomatic patients. The current study is one of the largest to suggest that there is room for additional novel risk stratification tools such as LV-GLS and

Zva, in addition to treadmill stress testing in asymptomatic severe AS patients.

The safety and utility of exercise testing in asymptomatic severe AS patients is well documented.^{16,43} As a result, AVR is recommended for patients with severe high-gradient AS who have symptoms on exercise testing (Class Ib) or an exercise-induced drop in systolic blood pressure (Class IIa).^{1,2} In a recent study, we have demonstrated that in asymptomatic patients with severe AS and LVEF, only 50% achieved 100% of AGP-METs; and exercise stress test provides significant reclassification of longer-term mortality risk, with higher achieved % AGP-METs associated with improved survival.¹⁶ In addition, there are reports demonstrating an association between Doppler echocardiographic findings (increased mean transaortic pressure and inadequate contractile reserve) and adverse prognosis in these patients.^{11,44}

AS patients develop LV hypertrophy to compensate for increased wall stress and to maintain systolic function. However, resting systolic function traditionally measured by LVEF eventually drops and in this setting, AVR is recommended to improve survival.^{1,2} Therefore, objective and reproducible parameters that identify early LV dysfunction, before a drop in LVEF could potentially allow more appropriate

Table 4. Synergistic and Incremental Prognostic Utility of Relevant Variables for Longer-Term All-Cause Mortality

	C-Statistic	P Value	NRI (95% CI)	P Value
(A) Entire study sample (N=504)				
STS score+% age-sex predicted METs	0.65 (0.56–0.73)	<0.001	0.40 (0.22–0.58)	<0.001
STS score+% age-sex predicted METs+ZVa	0.69 (0.61–0.78)	<0.01	0.26 (0.08–0.45)	<0.001
STS score+% age-sex predicted METs+ZVa+LV-GLS	0.75 (0.70–0.81)	<0.001	0.57 (0.39–0.74)	<0.001
STS score+% age-sex predicted METs+ZVa+LV-GLS+AVR	0.82 (0.75–0.86)	<0.001	0.27 (0.11–0.43)	<0.001
	C-Statistic	P Value	NRI	P Value
(B) Subgroup that underwent aortic valve replacement in follow-up (n=323)				
STS score+% age-sex predicted METs	0.60 (0.52–0.71)	0.02	0.33 (0.08–0.57)	0.009
STS score+% age-sex predicted METs+ZVa	0.66 (0.54–0.79)	0.01	0.43 (0.18–0.67)	0.005
STS score+% age-sex predicted METs+ZVa+LV-GLS	0.71 (0.63–0.79)	0.01	0.28 (0.04–0.53)	0.02

CI indicates confidence interval; LV-GLS, left ventricular global longitudinal strain; METs, metabolic equivalents; STS, Society of Thoracic Surgeons; Zva, valvuloarterial impedance.

timing of surgery and in turn, allow improved survival. Over the past decade, the relationship between global LV load and abnormal LV systolic performance in AS patients, even in those with preserved LVEF has become more apparent, and the use of novel echocardiographic measures of LV load (Zva)^{19,20,45} and LV systolic performance (LV-GLS)^{18,30,46} have been proposed as potential markers of early dysfunction, providing incremental prognostic utility.

It is also increasingly becoming evident that that a higher global LV load (quantified by Zva) is associated with progression of LV dysfunction (quantified by LV-GLS), even in situations where LVEF is preserved. Cramariuc et al. demonstrated

that abnormal stress corrected midwall shortening was seen in 10% of patients in the lowest versus 63% of patients in the highest tertile of Zva ($P<0.001$) in 1591 patients with asymptomatic severe AS and normal LVEF in the Simvastatin Ezetimibe in Aortic Stenosis trial.⁴⁷ Similarly in a study of 59 patients with asymptomatic severe AS, Zito et al. found that that increased Zva was associated with decreased LV-GLS with an r value of -0.56 , $P=0.016$.¹⁷ Our data further support a significant but weak association between Zva and LV-GLS among asymptomatic AS patients with normal LVEF.

Prior studies have also focused on Zva and LV-GLS to understand whether subtle changes in LV load and LV systolic

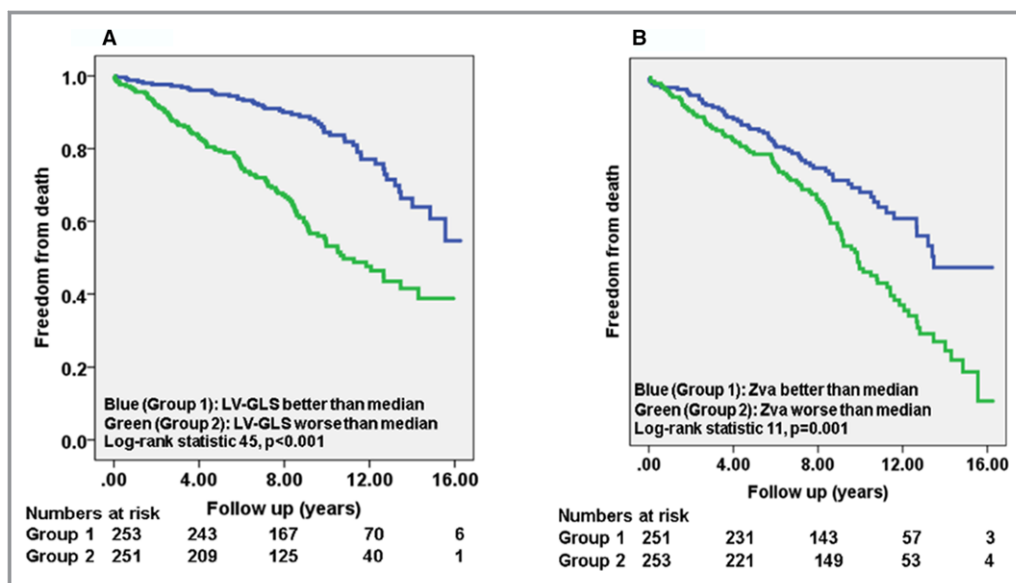


Figure 2. Kaplan–Meier survival curves in the study sample, separated on based on A) LV-GLS and B) Zva better or worse than median. LV-GLS=left ventricular global longitudinal strain, Zva=valvuloarterial impedance.

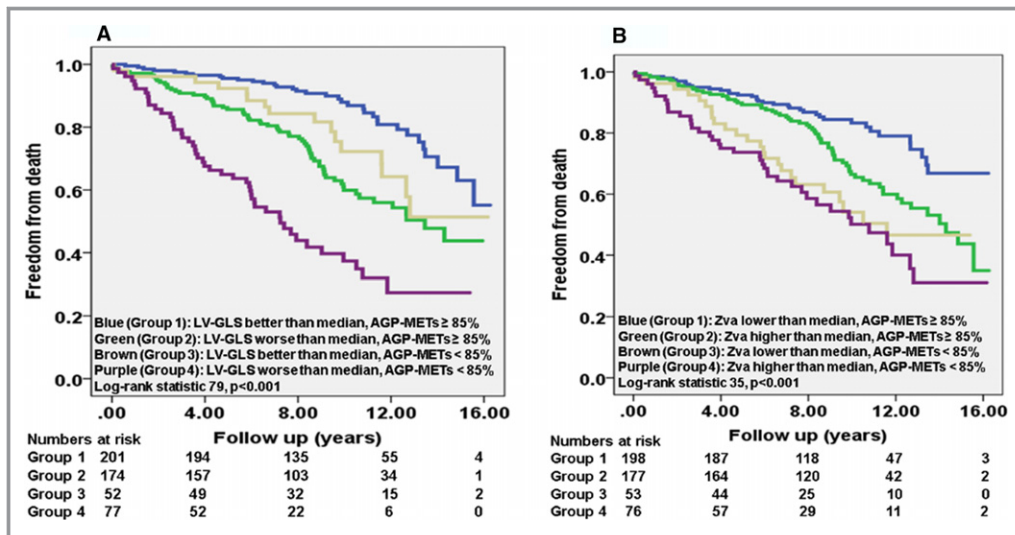


Figure 3. Kaplan–Meier survival curves in the study sample, separated on basis of A) 4 subgroups created based on LV-GLS (better or worse than median) and AGP-METs (higher or lower than 85%) and B) 4 subgroups created based on Zva (better or worse than median) and AGP-METs (higher or lower than 85%). LV-GLS=left ventricular global longitudinal strain, AGP-METs=age-sex predicted metabolic equivalents, Zva=valvuloarterial impedence.

performance can identify patients who will soon develop symptoms or cardiac events because of progressive AS with hemodynamic consequence impacting LV function.^{17–19} In one prior study of 79 patients with severe asymptomatic AS it was demonstrated that LV-GLS and Zva were both independently associated with survival at a mean of 23 months follow-up.¹⁸ Also, in 2 other small prior studies totaling 222 asymptomatic patients with severe AS, it was demonstrated

that Zva and LV-GLS were both independently associated with a combined end point of AS symptoms, AVR, or death.^{17,19} Despite similar findings in these 3 prior reports, each was limited by small sample size, lack of exercise testing data, and longer-term follow-up. The current study is one of the largest to demonstrate that Zva and LV-GLS offer incremental and synergistic prognostic utility beyond that which is detected by exercise testing alone in asymptomatic severe AS patients. It

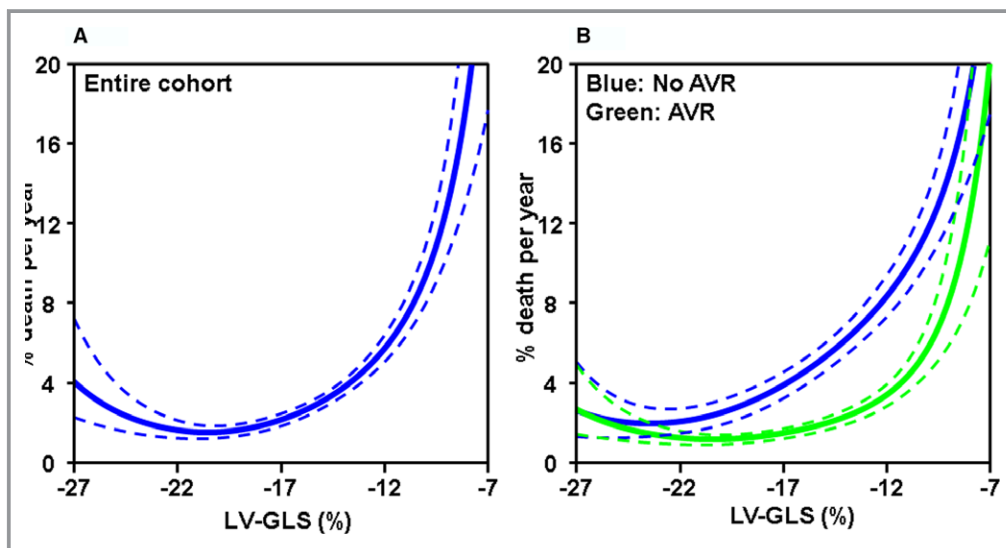


Figure 4. Quadratic spline analysis demonstrating a nomogram of estimated hazard rate at 5 years for LV-GLS. Panel A is for the study sample as a whole and panel B represents the study sample divided into 2 groups based on AVR vs no AVR during follow-up. Solid lines represent the 5-year parametric estimates, respectively, enclosed by 68% confidence interval (dashed lines). Please refer to text for details. LV-GLS=left ventricular global longitudinal strain, AVR=aortic valve replacement.

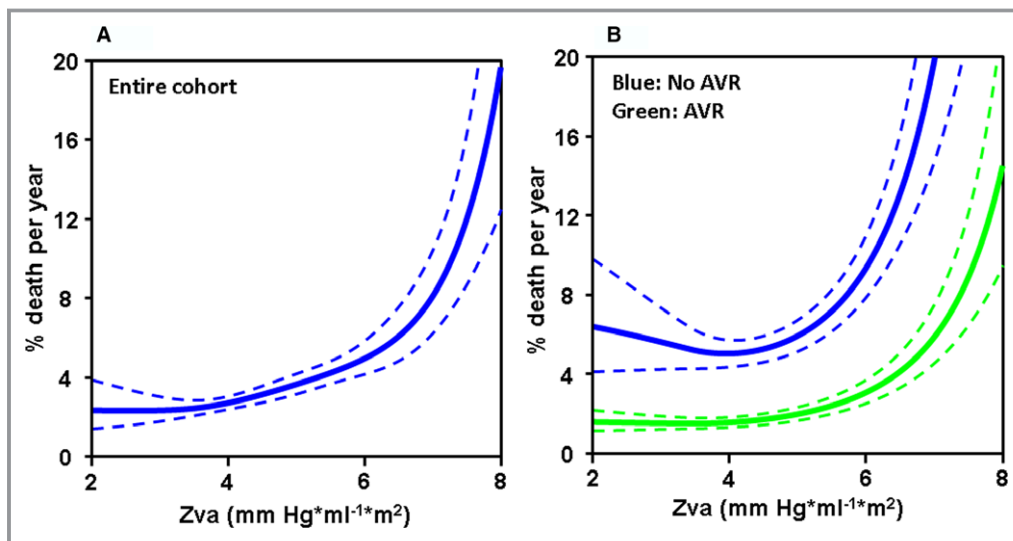


Figure 5. Quadratic spline analysis demonstrating a nomogram of estimated hazard rate at 5 years for Zva. Panel A is for the study sample as a whole and panel B represents the study sample divided into 2 groups based on AVR vs no AVR during follow-up. Solid lines represent the 5-year parametric estimates, respectively, enclosed by 68% confidence interval (dashed lines). Please refer to text for details. Zva=valvuloarterial impedence, AVR=aortic valve replacement.

appears that higher Zva (reflecting arterial and valvular load) would initially result in reduced LV-GLS (early systolic dysfunction) which could be reversed after an early AVR. However, a delay in AVR could potentially result in a more permanent reduction in LV-GLS, likely related to myocardial fibrosis. Indeed, in a previous publication, we have demonstrated that patients whose LV-GLS improves following AVR have a better longer-term prognosis versus those whose LV-GLS remains impaired.⁴⁸ One possibility for the permanent impairment in LV-GLS might be because of development of progressive myocardial fibrosis, which has been demonstrated previously.⁴⁹ It appears that once this has happened, Zva and LV-GLS potentially become synergistic in terms of their adverse impact on survival.

Limitations

It is a retrospective observational study with its inherent selection and referral biases. Some symptomatic patients achieving >85% AGP-METs were referred for AVR while some asymptomatic patients achieving <85% AGP-METs were treated conservatively, at the discretion of the treating physicians. It is also possible that the management and imaging techniques evolved over the duration of this study, as would be expected. It reports experience from a single tertiary care center that is well-experienced in managing these patients and the surgical results may not be replicated at lesser experienced centers. Because of significant reduction in statistical power, we did not divide the current sample into derivation and validation sets. In any case, these findings

need to be replicated in future prospective multicenter trials to avoid bias related to a single center. During follow up, only a small proportion of patients underwent isolated AVR, making this a heterogeneous population, where other factors like coronary artery disease and aortic disease could have affected outcomes. However, AS patients tend to be typically older with many co-morbidities, and our study reflects the current state of practice in most valve centers. However, the incremental prognostic utility of LV-GLS and Zva was preserved even in the subgroup of patients without documented obstructive coronary artery disease. Serum brain natriuretic peptide levels, known to be associated with outcomes in this population, were not routinely measured in the earlier part of this study and hence not reported. However, in a previous report, we have demonstrated its synergistic and incremental prognostic utility in patients with severe AS.⁵⁰ Also, we included patients over a broad time-frame and not all imaging data (AV gradients on peak stress echocardiography^{11,12} or AV calcium scoring on computed tomography) were available in all patients. As a prognostic cutoff, LV-GLS of -17% is higher than what has been previously reported by our institution in severe AS; however the current cohort was purely asymptomatic patients as opposed to the previous report.³⁰ The current study only reports associations, not causality. Post-exercise AV gradients were not routinely obtained in all patients, hence not reported in multivariable analysis. We report all-cause mortality as the primary end point, as opposed to cardiac mortality. However, on secondary outcomes analysis using competing risk regression, the basic results were similar. In any case, all-cause mortality is less biased than cardiac mortality.⁵¹

Conclusion

In asymptomatic patients with severe AS undergoing rest and exercise echocardiography, we demonstrate Zva and LV-GLS provide synergistic and incremental prognostic value in addition to functional capacity. While the role of AVR is well-accepted in symptomatic patients with severe AS, the use and timing of AVR in asymptomatic patients with severe AS remains uncertain. Our findings suggest that careful attention to sensitive markers such as Zva and LV-GLS, along with an evaluation of functional capacity, may potentially identify higher risk patients with apparently asymptomatic severe AS, thus aiding in optimal timing of AVR. However, these findings need to be replicated in future prospective studies.

Acknowledgments

Dr Desai is supported by the Haslam Family endowed chair in cardiovascular medicine. We acknowledge Penny Houghtaling PhD and Andrew Toth MS, Department of quantitative health sciences for statistical support of quadratic spline analysis.

Disclosures

Dr Marc Gillinov is on speakers' bureau for Atricure, Edwards, Medtronic and St. Jude's Medical and has an equity stake in Pleuraflow. Dr Johnston is a consultant for Edwards, St. Jude's, KEF Healthcare and iVHR. The remaining authors have no disclosures to report.

References

- Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Baron-Esquivias G, Baumgartner H, Borger MA, Carrel TP, De Bonis M, Evangelista A, Falk V, Lung B, Lancellotti P, Pierard L, Price S, Schafers HJ, Schuler G, Stepinska J, Swedberg K, Takkenberg J, Von Oppell UO, Windecker S, Zamorano JL, Zembala M. Guidelines on the management of valvular heart disease (version 2012): the Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur J Cardiothorac Surg*. 2012;42:S1–S44.
- Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP III, Fleisher LA, Jneid H, Mack MJ, McLeod CJ, O'Gara PT, Rigolin VH, Sundt TM III, Thompson A. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force On Clinical Practice Guidelines. *Circulation*. 2017;135:e1159–e1195.
- Otto CM, Burwash IG, Legget ME, Munt BI, Fujioka M, Healy NL, Kraft CD, Miyake-Hull CY, Schwaegler RG. Prospective study of asymptomatic valvular aortic stenosis. Clinical, echocardiographic, and exercise predictors of outcome. *Circulation*. 1997;95:2262–2270.
- Rosenhek R, Binder T, Porenta G, Lang I, Christ G, Schemper M, Maurer G, Baumgartner H. Predictors of outcome in severe, asymptomatic aortic stenosis. *N Engl J Med*. 2000;343:611–617.
- Rosenhek R, Zilberszac R, Schemper M, Czerny M, Mundigler G, Graf S, Bergler-Klein J, Grimm M, Gabriel H, Maurer G. Natural history of very severe aortic stenosis. *Circulation*. 2010;121:151–156.
- Pellikka PA, Sarano ME, Nishimura RA, Malouf JF, Bailey KR, Scott CG, Barnes ME, Tajik AJ. Outcome of 622 adults with asymptomatic, hemodynamically significant aortic stenosis during prolonged follow-up. *Circulation*. 2005;111:3290–3295.
- Dhoble A, Sarano ME, Kopecky SL, Thomas RJ, Hayes CL, Allison TG. Safety of symptom-limited cardiopulmonary exercise testing in patients with aortic stenosis. *Am J Med*. 125:704–708.
- Skalski J, Allison TG, Miller TD. The safety of cardiopulmonary exercise testing in a population with high-risk cardiovascular diseases. *Circulation*. 126:2465–2472.
- Das P, Rimington H, Chambers J. Exercise testing to stratify risk in aortic stenosis. *Eur Heart J*. 2005;26:1309–1313.
- Amato MC, Moffa PJ, Werner KE, Ramires JA. Treatment decision in asymptomatic aortic valve stenosis: role of exercise testing. *Heart*. 2001;86:381–386.
- Lancellotti P, Lebois F, Simon M, Tombeux C, Chauvel C, Pierard LA. Prognostic importance of quantitative exercise doppler echocardiography in asymptomatic valvular aortic stenosis. *Circulation*. 2005;112:1377–1382.
- Marechaux S, Hachicha Z, Belloquin A, Dumesnil JG, Meimoun P, Pasquet A, Bergeron S, Arsenault M, Le TOURNEAU T, Ennezat PV, Pibarot P. Usefulness of exercise-stress echocardiography for risk stratification of true asymptomatic patients with aortic valve stenosis. *Eur Heart J*. 31:1390–1397.
- Alborino D, Hoffmann JL, Fournet PC, Bloch A. Value of exercise testing to evaluate the indication for surgery in asymptomatic patients with valvular aortic stenosis. *J Heart Valve Dis*. 2002;11:204–209.
- Peidro R, Brion G, Angelino A. Exercise testing in asymptomatic aortic stenosis. *Cardiology*. 2007;108:258–264.
- Takeda S, Rimington H, Chambers J. Prediction of symptom-onset in aortic stenosis: a comparison of pressure drop/flow slope and haemodynamic measures at rest. *Int J Cardiol*. 2001;81:131–137; discussion 138–139.
- Masri A, Goodman AL, Barr T, Grimm RA, Sabik JF, Gillinov AM, Rodriguez LL, Svensson LG, Griffin BP, Desai MY. Predictors of long-term outcomes in asymptomatic patients with severe aortic stenosis and preserved left ventricular systolic function undergoing exercise echocardiography. *Circ Cardiovasc Imaging*. 2016;9:e004689.
- Zito C, Svalia J, Cusma-Piccione M, Antonini-Canterin F, Lentini S, Oretto G, Di Bella G, Montericcio V, Carerj S. Prognostic significance of valvuloarterial impedance and left ventricular longitudinal function in asymptomatic severe aortic stenosis involving three-cuspid valves. *Am J Cardiol*. 2011;108:1463–1469.
- Yingchoncharoen T, Gibby C, Rodriguez LL, Grimm RA, Marwick TH. Association of myocardial deformation with outcome in asymptomatic aortic stenosis with normal ejection fraction. *Circ Cardiovasc Imaging*. 2012;5:719–725.
- Lancellotti P, Donal E, Magne J, Moonen M, O'Connor K, Daubert JC, Pierard LA. Risk stratification in asymptomatic moderate to severe aortic stenosis: the importance of the valvular, arterial and ventricular interplay. *Heart*. 2010;96:1364–1371.
- Hachicha Z, Dumesnil JG, Pibarot P. Usefulness of the valvuloarterial impedance to predict adverse outcome in asymptomatic aortic stenosis. *J Am Coll Cardiol*. 2009;54:1003–1011.
- Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40:373–383.
- Baumgartner H, Hung J, Bermejo J, Chambers JB, Evangelista A, Griffin BP, Lung B, Otto CM, Pellikka PA, Quinones M. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. *J Am Soc Echocardiogr*. 2009;22:1–23; quiz 101–102.
- Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr*. 2005;18:1440–1463.
- Nagueh SF, Smiseth OA, Appleton CP, Byrd BF III, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P, Marino P, Oh JK, Popescu BA, Waggoner AD. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2016;29:277–314.
- Zoghbi WA, Enriquez-Sarano M, Foster E, Grayburn PA, Kraft CD, Levine RA, Nihoyannopoulos P, Otto CM, Quinones MA, Rakowski H, Stewart WJ, Waggoner A, Weissman NJ. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr*. 2003;16:777–802.
- Parikh R, Goodman AL, Barr T, Sabik JF, Svensson LG, Rodriguez LL, Lytle BW, Grimm RA, Griffin BP, Desai MY. Outcomes of surgical aortic valve replacement for severe aortic stenosis: incorporation of left ventricular

- systolic function and stroke volume index. *J Thorac Cardiovasc Surg.* 2015;149:1558–1566.e1551.
27. Dumesnil JG, Pibarot P, Carabello B. Paradoxical low flow and/or low gradient severe aortic stenosis despite preserved left ventricular ejection fraction: implications for diagnosis and treatment. *Eur Heart J.* 2010;31:281–289.
 28. Minners J, Allgeier M, Gohlke-Baerwolf C, Kienzle RP, Neumann FJ, Jander N. Inconsistencies of echocardiographic criteria for the grading of aortic valve stenosis. *Eur Heart J.* 2008;29:1043–1048.
 29. Pibarot P, Dumesnil JG. Low-flow, low-gradient aortic stenosis with normal and depressed left ventricular ejection fraction. *J Am Coll Cardiol.* 2012;60:1845–1853.
 30. Kusunose K, Goodman A, Parikh R, Barr T, Agarwal S, Popovic ZB, Grimm RA, Griffin BP, Desai MY. Incremental prognostic value of left ventricular global longitudinal strain in patients with aortic stenosis and preserved ejection fraction. *Circ Cardiovasc Imaging.* 2014;7:938–945.
 31. Cole CR, Blackstone EH, Pashkow FJ, Snader CE, Lauer MS. Heart-rate recovery immediately after exercise as a predictor of mortality. *N Engl J Med.* 1999;341:1351–1357.
 32. Morris CK, Myers J, Froelicher VF, Kawaguchi T, Ueshima K, Hideg A. Nomogram based on metabolic equivalents and age for assessing aerobic exercise capacity in men. *J Am Coll Cardiol.* 1993;22:175–182.
 33. Gulati M, Black HR, Shaw LJ, Arnsdorf MF, Merz CN, Lauer MS, Marwick TH, Pandey DK, Wicklund RH, Thisted RA. The prognostic value of a nomogram for exercise capacity in women. *N Engl J Med.* 2005;353:468–475.
 34. Kim ES, Ishwaran H, Blackstone E, Lauer MS. External prognostic validations and comparisons of age- and gender-adjusted exercise capacity predictions. *J Am Coll Cardiol.* 2007;50:1867–1875.
 35. Lauer MS, Francis GS, Okin PM, Pashkow FJ, Snader CE, Marwick TH. Impaired chronotropic response to exercise stress testing as a predictor of mortality. *JAMA.* 1999;281:524–529.
 36. Mark DB, Hlatky MA, Harrell FE Jr, Lee KL, Califf RM, Pryor DB. Exercise treadmill score for predicting prognosis in coronary artery disease. *Ann Intern Med.* 1987;106:793–800.
 37. Pellikka PA, Nagueh SF, Elhendy AA, Kuehl CA, Sawada SG. American society of echocardiography recommendations for performance, interpretation, and application of stress echocardiography. *J Am Soc Echocardiogr.* 2007;20:1021–1041.
 38. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc.* 1999;94:496–509.
 39. Mentias A, Feng K, Alashi A, Rodriguez LL, Gillinov AM, Johnston DR, Sabik JF, Svensson LG, Grimm RA, Griffin BP, Desai MY. Long-term outcomes in patients with aortic regurgitation and preserved left ventricular ejection fraction. *J Am Coll Cardiol.* 2016;68:2144–2153.
 40. Marechaux S, Hachicha Z, Bellouin A, Dumesnil JG, Meimoun P, Pasquet A, Bergeron S, Arsenault M, Le Tourneau T, Ennezat PV, Pibarot P. Usefulness of exercise-stress echocardiography for risk stratification of true asymptomatic patients with aortic valve stenosis. *Eur Heart J.* 2010;31:1390–1397.
 41. Lim WY, Ramasamy A, Lloyd G, Bhattacharyya S. Meta-analysis of the impact of intervention versus symptom-driven management in asymptomatic severe aortic stenosis. *Heart.* 2017;103:268–272.
 42. Shirai S, Taniguchi T, Morimoto T, Ando K, Korai K, Minakata K, Hanyu M, Yamazaki F, Koyama T, Komiya T, Kanamori N, Murata K, Kitai T, Kawase Y, Izumi C, Inada T, Minamino-Muta E, Kato T, Inoko M, Ishii K, Saito N, Yamanaka K, Nishiwaki N, Nakajima H, Saga T, Nakayama S, Sakaguchi G, Iwakura A, Shiraga K, Ueyama K, Fujiwara K, Miwa S, Nishizawa J, Kitano M, Kitayama H, Sakata R, Kimura T. Five-year clinical outcome of asymptomatic vs. symptomatic severe aortic stenosis after aortic valve replacement. *Circ J.* 2017;81:485–494.
 43. Rafique AM, Biner S, Ray I, Forrester JS, Tolstrup K, Siegel RJ. Meta-analysis of prognostic value of stress testing in patients with asymptomatic severe aortic stenosis. *Am J Cardiol.* 2009;104:972–977.
 44. Weisenberg D, Shapira Y, Vaturi M, Monakier D, Iakobishvili Z, Battler A, Sagie A. Does exercise echocardiography have an added value over exercise testing alone in asymptomatic patients with severe aortic stenosis? *J Heart Valve Dis.* 2008;17:376–380.
 45. Briand M, Dumesnil JG, Kadem L, Tongue AG, Rieu R, Garcia D, Pibarot P. Reduced systemic arterial compliance impacts significantly on left ventricular afterload and function in aortic stenosis: implications for diagnosis and treatment. *J Am Coll Cardiol.* 2005;46:291–298.
 46. Delgado V, Tops LF, van Bommel RJ, van der Kleij F, Marsan NA, Klautz RJ, Versteegh MI, Holman ER, Schaliij MJ, Bax JJ. Strain analysis in patients with severe aortic stenosis and preserved left ventricular ejection fraction undergoing surgical valve replacement. *Eur Heart J.* 2009;30:3037–3047.
 47. Cramariuc D, Cioffi G, Rieck AE, Devereux RB, Staal EM, Ray S, Wachtell K, Gerds E. Low-flow aortic stenosis in asymptomatic patients: valvular-arterial impedance and systolic function from the seas substudy. *JACC Cardiovasc Imaging.* 2009;2:390–399.
 48. Kafa R, Kusunose K, Goodman AL, Svensson LG, Sabik JF, Griffin BP, Desai MY. Association of abnormal postoperative left ventricular global longitudinal strain with outcomes in severe aortic stenosis following aortic valve replacement. *JAMA Cardiol.* 2016;1:494–496.
 49. Azevedo CF, Nigri M, Higuchi ML, Pomerantzeff PM, Spina GS, Sampaio RO, Tarasoutchi F, Grinberg M, Rochitte CE. Prognostic significance of myocardial fibrosis quantification by histopathology and magnetic resonance imaging in patients with severe aortic valve disease. *J Am Coll Cardiol.* 2016;57:278–287.
 50. Goodman A, Kusunose K, Popovic ZB, Parikh R, Barr T, Sabik JF, Rodriguez LL, Svensson LG, Griffin BP, Desai MY. Synergistic utility of brain natriuretic peptide and left ventricular strain in patients with significant aortic stenosis. *J Am Heart Assoc.* 2016;5:e002561. DOI: 10.1161/JAHA.115.002561.
 51. Lauer MS, Blackstone EH, Young JB, Topol EJ. Cause of death in clinical research: time for a reassessment? *J Am Coll Cardiol.* 1999;34:618–620.

Supplemental Material

Data S1.

Additional survival analysis

Following stratification of the subgroup without documented CAD (n=338, number of longer-term deaths=98), the findings of multivariable Cox Proportional Hazard analysis were similar. Higher STS score (HR 1.03 [95% CI 1.01-1.18]), lower % AGP-METS (HR 1.09 [95% CI 1.03-1.27]), slower HRR (HR 1.09 [95% CI 1.03-1.29]), lower LV-GLS (HR 1.06 [1.02-1.11]) and higher Zva (HR 1.12 [95% CI 1.02-1.41]) were associated with higher longer-term mortality, while AVR (time dependent covariate, HR 0.61 [95% CI 0.42-0.89]) was associated with improved survival (all p <0.05).

In the entire study sample, the data on multivariable competing risk regression analysis based on the Fine-Gray proportional subhazards model for longer-term cardiac deaths (cardiac deaths=148, documented noncardiac deaths=16) revealed that higher STS score (sub hazard ratio or sHR 1.04 [95% CI 1.02-1.16]), lower % AGP-METS (sHR 1.21 [95% CI 1.07-1.28]), slower HRR (sHR 1.12 [95% CI 1.04-1.40]), lower LV-GLS (sHR 1.09 [1.04-1.22]) and higher Zva (sHR 1.19 [95% CI 1.02-1.51]) were associated with higher longer-term cardiac deaths, while AVR, sHR 0.51 [95% CI 0.40-0.85]) was associated with improved survival (all p <0.01).

Supplemental subgroup Kaplan-Meier survival analysis

We subsequently created 4 subgroups, divided on basis of achieving $\geq 85\%$ AGP-METs and subsequent AVR vs. no AVR. The proportion of deaths in these 4 subgroups were significantly different (log-rank p<0.001), as follows: a) AGP-METs $\geq 85\%$, AVR [55/249 (22%)] b) AGP-

METs <85%, AVR [29/74 (39%)] c) AGP-METs \geq 85%, no AVR [46/126(37%)] and d) AGP-METs <85%, no AVR [34/55 (62%)].

The proportion of deaths in 4 subgroups, based on median Zva and LV-GLS, were significantly different (log-rank 50, $p < 0.001$), as follows: a) both LV-GLS and Zva better than median [19/146 (13%)] b) LV-GLS better than median, Zva worse than median [31/107 (29%)] c) LV-GLS worse than median, Zva better than median [42/105 (40%)] and d) both LV-GLS and Zva worse than median [72/146 (49%)]. The Kaplan-Meier curves are shown in Figure S1a. The proportion of deaths in 4 subgroups, based on either LV-GLS and/or Zva better than median and AVR during follow-up, were significantly different (log-rank 66, $p < 0.001$), as follows: a) LV-GLS and Zva better than median, AVR [46/241 (19%)] b) Either LV-GLS and/or Zva worse than median, AVR [38/82 (46%)] c) Both LV-GLS and Zva better than median, no AVR [46/117 (39%)] and d) Either LV-GLS and/or Zva worse than median, no AVR [36/64 (53%)]. The Kaplan-Meier curves are shown in Figure S1b.

Table S1. Relevant characteristics of the study sample, separated on basis of LV-GLS better or worse than median.

Variable	LV-GLS better than median (n=253)	LV-GLS worse than median (n=251)	p-value
Age (years)	65±12	66±13	0.27
Male sex	193 (76 %)	199 (79%)	0.42
Hypertension	177 (70%)	181 (72%)	0.59
Obstructive CAD	76 (30%)	84 (33%)	0.41
STS score	2.81±3	2.95±3	0.63
LV ejection fraction (%)	58±5	57±3	0.18
Indexed LV mass (g/m²)	112±59	121±66	0.12
Peak gradient (mm Hg)	59±17	58±19	0.32
Mean AV gradient (mm Hg)	35±11	35±12	0.62
Stroke volume index (ml/m²)	40±10	39±9	0.12
Zva	4.33±0.9	4.70±0.9	<0.001
≥ Moderate aortic regurgitation	54 (21%)	50 (20%)	0.39
Resting RVSP (mm Hg)	33±7	34±9	0.11
Peak rate pressure product	23255±5466	22562±5589	0.16
% maximum predicted heart rate achieved	88±12	87±13	0.37
Chronotropic response index	0.80±0.2	0.78±0.2	0.20
Maximum METs	8.2±3	7.2±2	<0.001
<85% age-sex predicted METs	52 (21%)	77 (30%)	0.006
≥1 ischemic LV territories	27 (11%)	31 (12%)	0.58
Post-stress RVSP	48±20	49±19	0.42

METs=metabolic equivalents, CAD= coronary artery disease, ACE=angiotensin converting enzyme, STS=Society of thoracic surgeons
p-values reflect comparison between subgroups

Table S2. Relevant characteristics of the study sample, separated on basis of Zva better or worse than median.

Variable	Zva better than median (n=251)	Zva worse than median (n=253)	p-value
Age (years)	66±12	66±13	0.71
Male sex	190 (76 %)	200 (80%)	0.37
Hypertension	165 (68%)	193(74%)	0.009
Obstructive CAD	78 (31%)	82(32%)	0.75
STS score	3.0±3	2.7±3	0.27
LV ejection fraction (%)	58±4	57±4	0.32
Indexed LV mass (g/m²)	117±33	113±38	0.47
Peak gradient (mm Hg)	63±17	54±17	<0.001
Mean AV gradient (mm Hg)	39±12	32±9	<0.001
Stroke volume index (ml/m²)	45±9	34±4	<0.001
LV-GLS (%)	-16.8±4	-15.3±4	<0.001
≥ Moderate aortic regurgitation	55 (22%)	49 (19%)	0.48
Resting RVSP (mm Hg)	33±9	34±10	0.34
Peak rate pressure product	22512±5436	23307±5609	0.11
% maximum predicted heart rate	87±12	88±13	0.38
Chronotropic response index	0.78±0.2	0.79±0.2	0.76
Maximum METs	8.1±3	7.3±2	<0.001
<85% age-sex predicted METs	53 (21%)	76 (30%)	0.01
≥ ischemic LV territories	28 (11%)	30 (12%)	0.80
Post-stress RVSP	48±21	49±18	0.45

Figure S1. Kaplan-Meier survival curves in the study sample, separated on basis of a) 4 subgroups created based on LV-GLS and Zva better or worse than median and b) LV-GLS/ZVa better or worse than median and AVR during follow-up.

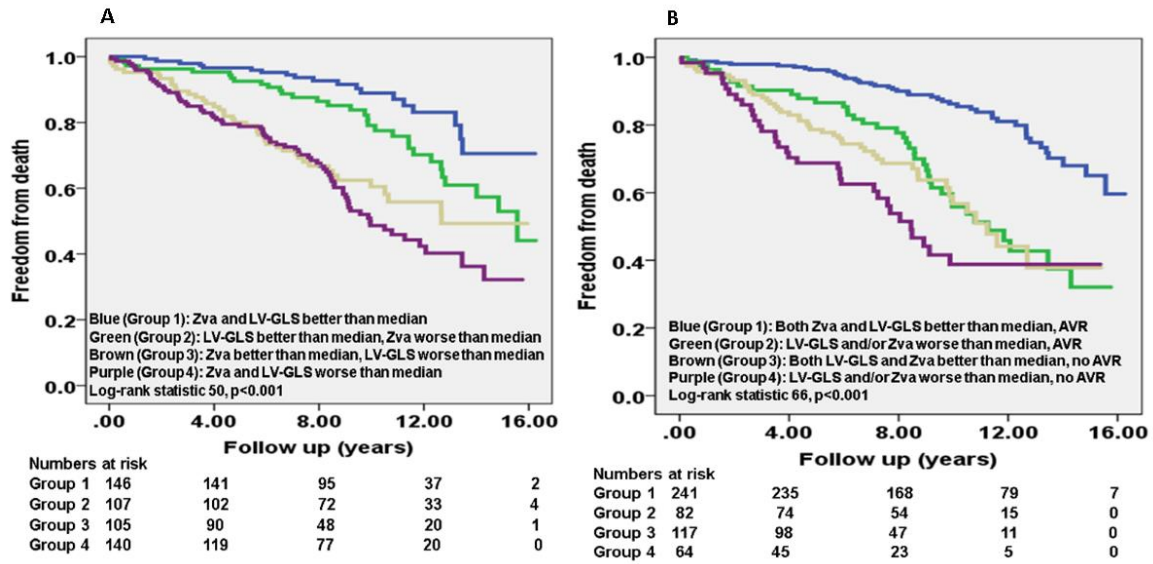
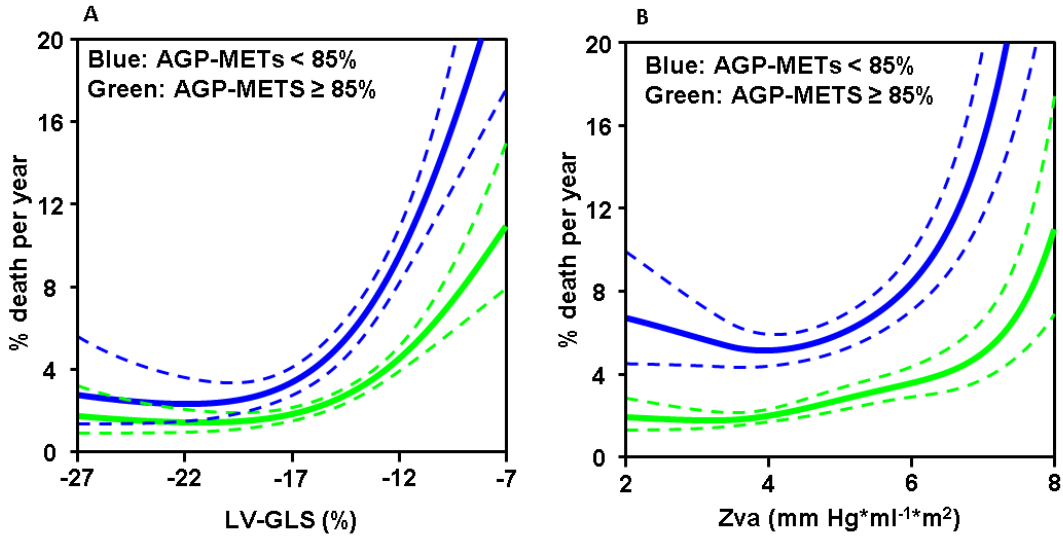


Figure S2. Supplemental Quadratic spline analysis.



Quadratic spline analysis demonstrating a nomogram of estimated hazard rate at 5 years for LV-GLS and Zva. Figure S2A is for the increasing hazard of death/year with worsening LV-GLS in the study sample divided on the basis of AGP-METS higher or lower than 85%. Figure S2B is for the increasing hazard of death with worsening Zva in the study sample divided on the basis of AGP-METS higher or lower than 85%. Solid lines represent the 5-year parametric estimates, respectively, enclosed by 68% confidence interval (dashed lines).

We demonstrate that the cutoff of LV-GLS which was associated with an increased risk of death in the whole cohort, was different in patients with AGP-Mets higher vs. lower than 85% (A). Similarly, the cutoff of LV-GLS which was associated with an increased risk of death in the whole cohort, was different in patients with AGP-Mets higher vs. lower than 85% (B).