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First-phase ejection fraction is a powerful predictor of adverse events in asymptomatic patients with aortic stenosis and preserved total ejection fraction

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Abstract
Objectives We examined the prognostic value of first-phase ejection fraction (EF1) in patients with aortic stenosis (AS), a condition in which left ventricular dysfunction as measured by conventional indices is an indication for valve replacement.
Background EF1, the ejection fraction up to the time of maximal ventricular contraction may be more sensitive than existing markers in detecting early systolic dysfunction.
Methods The predictive value of EF1 compared to conventional echocardiographic indices for outcomes was assessed in 218 asymptomatic patients with at least moderate AS, including 73 with moderate, 50 with severe and 96 with "discordant" (aortic area < 1.0 cm^2 and gradient < 40 mmHg) AS, all with preserved EF, followed for at least 2 years. EF1 was measured retrospectively from archived echocardiographic images by wall tracking of the endocardium. The primary outcome was a combined event of aortic valve intervention, hospitalisation for heart failure and death from any cause.
Results EF1 was the most powerful predictor of events in the total population and all sub-groups. A cut-off value of 25% gave hazard ratios (for EF1<25% compared to ≥25%) of 27.7, (95% confidence interval 13.1-58.7, P<0.001) unadjusted, and 24.4 (11.3-52.7, P<0.001) adjusted for other echocardiographic measures including global longitudinal strain, for events at 2-years in all patients with asymptomatic AS. Corresponding hazard ratios for all-cause mortality in the total population were 17.5 (5.7-53.3) and 17.4 (5.5-55.2) unadjusted and adjusted respectively.
Conclusion EF1 may be potentially valuable in the clinical management of patients with AS and other conditions in which there is progression from early to late systolic dysfunction.

Key Words: ejection fraction, aortic stenosis, myocardial function

Abbreviations list:
AS: aortic stenosis
AUC: area under the curve
AVA: effective aortic valve area
AVR: aortic valve replacement
EF1: first-phase ejection fraction
GLS: global longitudinal strain
LVM: left ventricular mass
MPG: mean pressure gradient
ROC: receiver operating characteristic
SV: stroke volume
TAFR: trans-aortic flow rate
TPAVF: time to peak aortic valve flow

Introduction

Aortic stenosis (AS) is the most common form of primary heart valve disease in more economically developed countries, with a prevalence of moderate or severe disease of approximately 3% aged ≥75 (1). It is often asymptomatic but when symptoms develop and/or there is a reduction in left ventricular (LV) ejection fraction (EF), survival without intervention is poor (2). Symptoms or reduced EF are thus Class I indications for aortic valve replacement (AVR) in severe AS while the management of asymptomatic severe AS remains less certain (3-5), particularly for patients in whom measures of AS severity by valve area and pressure gradient are "discordant" (6,7). The mortality soon after the onset of symptoms before surgery can be performed is up to 15% (8). An objective measurement that predicts impairment in EF and/or imminent onset of symptoms would thus be invaluable in selecting high-risk asymptomatic patients with preserved EF for more frequent clinical monitoring or early surgical intervention.

The biophysics of myocyte contraction suggest that, when systolic function is impaired early in systole, a mechanism may exist to preserve overall LV EF at the expense of a slower sustained contraction (9-11). A novel measure of early ejection fraction is the first-phase ejection fraction (EF1, Figure 1), the ejection fraction up to the time of maximal ventricular fibre shortening. This may be a fundamental characteristic of LV function that determines subsequent events in systole via mechanosensing (10). In a pilot study, we observed a marked impairment of EF1 in AS, despite preserved overall EF. EF1 was inversely related to the severity of the AS suggesting it could be a sensitive prognostic marker of future systolic function and subsequent events in AS. The purpose of the present study was to examine the value of EF1 in predicting the onset of symptoms requiring valve intervention or major events in a cohort of patients with moderate to severe AS. We compared EF1 with conventional measures of valve and LV function.

Methods

Patient population

A retrospective study of the predictive value of EF1 for major adverse cardiovascular events was undertaken in consecutive asymptomatic patients with at least moderate AS seen in a specialist valve clinic at Guy's and St Thomas' Hospital between January 2008 and December 2015 using anonymised data from the Guy's and St Thomas' Valve Study Group. This included demographics, symptoms and risk factors including smoking, hypertension, diabetes, coronary artery disease (defined as a history of angina pectoris or evidence of a > 50% coronary artery stenosis on angiography) and chronic kidney disease as well as outcome data for all patients.

All patient clinical records were entered in a hospital digital database (Electronic Patient Record, iSOFT Group, Aldershot, UK). Outcome data were verified from Hospital records. Symptoms were carefully evaluated by one of the authors (JC) at the time of presentation and for patients in whom symptoms were uncertain, an exercise tolerance test was performed. Inclusion criteria comprised asymptomatic AS of at least moderate severity with LV EF ≥ 50%. Exclusion criteria included: resting arrhythmia, more than moderate disease of other valves, lost to follow-up and suboptimal ultrasound images. The primary outcome was a combination of aortic valve intervention (as a result of developing symptoms or EF < 50%), hospitalisation for heart failure and all-cause mortality. All-cause mortality was examined as a secondary outcome.

Echocardiography and first phase ejection fraction

Transthoracic echocardiography was performed with patients at rest using a GE Vivid 7 ultrasound platform (GE Healthcare, Andover, USA). All echocardiographic measurements were performed using standard techniques according to the recommendations of the American society of Echocardiography (12). LV mass was measured from a two-dimensional

parasternal view according to ASE recommendations. LV mass index (LVM/LVMi) was calculated by dividing LVM by body surface area (BSA). Left atrial (LA) volume was measured by tracing the LA border from apical 4 and 2 chamber views and left atrial volume index (LAVi) obtained by indexing LA volume to BSA. Stroke volume was calculated as volume difference between ED and ES and indexed to BSA to give stroke volume index (SV/SVi). Trans-aortic flow rate (TAFR) was defined as stroke volume over ejection time (ET). Tissue Doppler measures were obtained at levels of the lateral and septal mitral annulus to obtain an optimal spectral Doppler waveform. The E/e' ratio was calculated as a measure of diastolic function from the ratio of the transmitral Doppler E wave velocity to the mean of basal lateral and septal tissue Doppler e' waves (13). Effective aortic orifice area was calculated using the continuity equation and indexed to BSA (AVA/AVAi). Moderate AS was defined as peak AV velocity 3.0-4.0m/s, mean pressure gradient (MPG) 20-40mmHg, and AVA 1.0-1.5cm^2; severe AS was defined as peak AV velocity > 4.0m/s, MPG >40mmHg, and aortic valve area <1.0cm^2. Patients with MPG<40mmHg and AVA<1.0cm^2 were defined as "discordant" (6,7). Current algorithms (14,15) further divide this discordant group by SVi with a cut-point of 35 mL/m^2 as a surrogate for flow. In this study, we divided them by calculated trans-aortic flow rate (< and > 200mL/ms) (16) as well as SVi and also by EF1 and global longitudinal strain (GLS) as further measures of LV dysfunction using cut-points derived from receiver-operating characteristic (ROC) curve analysis as described below.

The additional image analysis was performed by two authors whilst blinded to clinical outcomes on archived images using the EchoPAC analysis package (EchoPAC, GE Healthcare, Guildford, UK). GLS was measured by from speckle tracking echocardiography by placing 6 points along endocardial border and adjusting the width of interest to accommodate myocardial thickness from apical 4, 2 and 3 chamber views. LV volumes were

measured by 2D Simpson's method from apical 4 and 2 chamber views at end-diastole, time of peak aortic valve flow and end-systole. Ejection Fraction (EF) was calculated as the percentage change of LV volume from end-diastole to end-systole. EF1 was taken as the percentage change in LV volume from end-diastole to the time of peak AV flow (TPAVF, Figure 1), a time that approximates the time of peak ventricular contraction in individual myocytes. EF1 was thus given by: EF 1= (EDV –V1) / EDV x 100 %
where EDV is end-diastolic volume and V1 is volume at time of peak AV flow.

Intra- and inter-observer variability in measurements of EF1 was assessed in 18 randomly selected subjects by measurements repeated 2 months apart by 2 observers with the coefficient of variation defined as the standard deviation of difference in measures expressed as a percentage of the mean measurement.

Statistical Analysis

Continuous variables were tested for normality, and those following a Gaussian distribution were presented as means±standard deviation (SD). Other variables were presented as medians and inter-quartile range. Comparisons between groups were made by Student's *t*-test for continuous variables or by χ^2 test for categorical variables. Receiver-operating characteristic analysis was performed to examine the sensitivity and specificity of measures for events and the best cut-off value for predicting events was determined to maximise values of sensitivity and specificity. Kaplan-Meier curves were used to examine cumulative event rates and the difference between groups was tested using a log rank test. Univariate Cox regression analysis was performed to identify potential predictors of events. Multivariate Cox proportional hazards models were used to test the independent value of echocardiographic measures for predicting future events. Analyses were repeated for the total population and in patients with moderate, severe, and discordant AS and in patients with EF in the lowest tertile. A two-tailed P-value of <0.05 was considered statistically significant. We assessed hazard ratios after 2

years of follow-up because this is a timeframe over which risk would inform clinical management (and ultimately all patients have events). All above statistical analyses were performed using SPSS 24 for Mac (SPSS Inc. Chicago, IL, USA). Categorical net reclassification improvement (assessed using the R software packages SurvIDINRI V1.1-1, Hajime Uno) was used to determine the added value of EF1 to conventional indices in predicting events.

Results

Patient characteristics and major events

Three hundred and thirty-three patients meeting the inclusion criteria were identified of which 115 were excluded from the final analysis, due to arrhythmias (n=28), more than moderate valve disease other than AS (n=37), loss to follow-up (n=21) and suboptimal echo image (n=29) (Figure 2). Thus, a total of 218 asymptomatic patients including 73 (33.5%) with moderate AS, 49 (22.5%) with severe AS and 96 (44.0%) with discordant AS were included in the final analysis. The aetiology of AS was degenerative 82.1%, congenital (bicuspid aortic valve) 17.4%, and uncertain 0.5%. The majority of patients who developed symptoms (n=102) during follow-up either underwent AVR (88/102) or died (11/102) whilst waiting for surgery shortly after developing symptoms. Only 3 patients developed symptoms without having AVR (because of unacceptable risk). In total 143 (65.6%) patients experienced an event after a median follow up of 33.4 months (IQR 21.0-51.2 months), including 89 (40.8%) surgical AVR, 17 (7.8%) transaortic AVR, 3 (1.4%) balloon aortic valvuloplasty, 2 (0.9%) hospitalisation due to heart failure and 32 (14.7%) death (before AVR or valvuloplasy). In patients with coronary artery disease, 13 had both CABG and AVR but the primary indication for surgery was AVR in all 13 patients. Event-free survival was 70.6%, 43.1% and 17.0% at 2, 3 and 5 years respectively. The proportion of patients experiencing events was related to

the severity of AS (47.9%, 89.8% and 66.7% in patients with moderate, severe and discordant AS, respectively).

EF1 and other echocardiographic measures

Baseline clinical characteristics and echocardiographic data of patients with moderate, severe and discordant AS according to events are shown in Table 1. EF and GLS were not significantly different in the three groups. The intra-observer and inter-observer coefficients of variation for EF1 were 6.7±3.6% and 9.8±6.1%, respectively. Absolute difference in EF1 was 2.9% and 2.1% between and amongst observers (Figure S2). EF1 was negatively associated with AV MPG (β=-0.192, p=0.005) with or without adjustment for age, gender, EF, GLS, LVMi and TPAVF/ejection time ratio. EF1 was the lowest in patients with severe AS (24.8±11.7%), compared to those with discordant (27.8±9.5%) and moderate AS (30.8±9.2%).

When comparing those with events to those without events, EF1 was reduced in all 3 groups and, in those with severe and discordant AS, was the only measure of systolic function that was reduced. In patients with moderate AS, MPG was significantly greater and AVAi smaller in patients with compared to those without events; SVi was significantly lower and GLS was significantly impaired in those with events compared to those without events. The percentage of patients with coronary artery disease and chronic kidney disease was also higher in those with events compared to those without events (Table 1).

Prediction of major events by EF1 and other echocardiographic measures

ROC curve analyses of EF1, GLS, MPG, AVAi, SVi and TAFR for predicting the primary outcome at 2 years are shown in Figure 3. The area under the curve (AUC) was the largest for EF1 (0.927, p<0.0001), followed by EF, MPG, GLS, AVAi, SVi and TAFR and the AUC for EF1 was significantly greater than that for the other predictors (p<0.0001). A cut-off value of 25% for EF1 had a sensitivity of 87.1% and a specificity of 90.0% for prediction of events.

For GLS a cut off-value of -15% had a sensitivity of 56.5% and a specificity of 66.7%. The incremental value of EF1 to a model including EF, GLS, LVMi and MPG, in terms of net reclassification was 67.3 % (95% confidence interval [CI]: 50.5-77.7%, p<0.001).

Kaplan-Meier analysis showed that EF1 was a strong predictor of events in the total population over the whole follow-up period (Figure 4a). When EF1 was less than 25%, the 1-year, 2-year and 5-year event rates were 36.2%, 78.3% and 94.2%, respectively, compared to 1.3%, 6.7% and 77.9% in patients with EF1≥25%. When comparing tertiles of the distribution of EF1, only 2/72 (2.8%) patients in the upper tertile had an event at 2 years whereas 53/73 (72.6%) of patients in the lower tertile had events. EF1 was a stronger predictor of events than GLS (Figure S1). EF1 had strong predictive value in all patients irrespective of severity (moderate, severe or discordant, Figure 4b-4d). In the discordant group, EF1 was a stronger predictor of events (p<0.001) than GLS (p=0.049, Figure 5a), SVi or TAFR (Figure 5b and 5c).

On univariate Cox regression analysis several measures of AS severity (MPG and AVAi) and of LV systolic function (EF, GLS and SVi) as well as LVMi, LAVi and TPAVF (table 2) were related to events at 2-years in the the total population. However, EF1 was more strongly related to events and the hazard ratio for each 1% increase in EF1 was 0.888 (95% CI: 0.865-0.911, p<0.001). Heart rate and ejection time were not significantly related to events, with TPAVF the only timing variable significantly related to events. In multivariate models 1 the independent predictive values of EF1 with GLS, MPG and LVMi were tested. In the total population, both MPG and EF1 were independently predictive of events but EF1 was more strongly predictive than MPG (table 2). In model 2, when all significant predictors in univariate analysis were entered, EF1 remained the most significant predictor of events (table 2) with the hazard ratio for EF1 unchanged despite adjustment for these additional variables. This was also the case when measures of systolic function were added sequentially in a

forward step-wise analysis (tables S2). When an alternate end-point comprising symptoms, hospitalisation or death was considered hazard ratios were unchanged (HR: 0.882, 95% CI: 0.860-0.906; p<0.001 compared to 0.885, 95% CI 0.863-0.903, p<0.001 when AVR was used in the end-point).

When considering EF1 as a categorical variable (EF1< 25% vs. EF1 ≥ 25%) the HR was 27.7 (95%CI:13.1-58.7, P<0.001) unadjusted and 24.4 (95%CI:11.3-52.7, P<0.001), adjusted for other echocardiographic measures including GLS, for 2-year events in the total population. In patients with EF in the lowest tertile, EF1 remained as the strongest predictor (HR: 0.846, 95% CI: 0.802-0.894, p<0.001). Forcing heart rate or ejection time into the final model made no significant difference to the predictive value of EF1 (data not shown).

EF1 was also the strongest predictor of events in all groups with a similar HR to that in the total population. In the discordant group, EF1 was the only significant predictor of events (HR: 0.897, 95% CI: 0.866-0.930, p<0.001, table 2) and in patients with moderate and severe AS, EF1 remained a strong predictor in both univariate and multivariable models (table S1).

Prediction of All-cause mortality

Thirty-two patients died before intervention with a median follow up of 20.8 months (IQR 13.7-34.8 months). One-year and two-year mortality rates in all patients with a reduced EF1 (<25%) were 7.2% (n=5) and 21.7% (n=15) compared with 0.7% (n=1) and 2.7% (n=4) in patients with EF1≥25% (log rank 46.3, P<0.0001, Figure 6). HR for all-cause mortality at 2 years for EF1< 25% vs. EF1 ≥ 25% in the total population were 17.5 (5.7-53.3) unadjusted and 17.4 (5.5-55.2) when adjusted for MPG, GLS, LVMi and TAFR. TAFR had modest predictive value for all-cause mortality in univariate cox regression analysis (HR 0.993 (0.986-0.999), P=0.018) but was not significantly associated with mortality when EF1 was included in the multivariate model.

Discussion

In the present study we hypothesised that, in patients with asymptomatic AS and preserved EF, EF1, a measure of early systolic function up to the time of maximal AV flow, would have greater prognostic impact than measures calculated to end-systole. We showed a striking hazard ratio of 27.7 (95% CI: 13.1-58.7) for EF1<25% in predicting a major event within 2 years of presentation. EF1 was superior to 2D GLS and other measures of LV or aortic valve function (including newer indices of valve function derived from timing of aortic valve flow such as TPAVF (17)). There is a trend towards prophylactic surgery in asymptomatic severe AS (18,19) and it is possible that EF1 could be used to guide this decision.

EF1 was equally strongly predictive of events in groups classified as moderate, severe and discordant. Within the discordant group, current guidelines advocate the use of SVi to sub-divide this group into moderate or low-flow severe AS (3,14,15). However, we found no predictive value of SVi within this group. Similarly, other measures of LV systolic function, flow rate, and GLS did not predict events in the discordant group. This may be because these measures are calculated over the whole of systole and do not capture the reduction in early systolic function which we have shown is prognostically important. A surprising finding was that EF1 was predictive of major events in patients with moderate AS. Only a minority of patients with high-gradient severe AS are thought to progress to low-flow, low gradient severe AS (20) and it is known that LV function can be affected by coronary artery disease and other risk factors (21,22). The present study provides further corroborative evidence that LV systolic function can change independently of valve function, and it is notable that in our study patients with moderate AS and major events had a higher prevalence of CAD than those without events.

Whilst our primary outcome was the prediction of events in asymptomatic patients with AS, it is notable that EF1 was also predictive of all-cause mortality in the total population, so that 2-year mortality for all patients in the lowest tertile of EF1 was 21.7%, compared to 2.7% for patients with EF1 in the highest tertile. That TAFR was predictive of all-cause mortality when considered alone but not when in addition to EF1 is consistent with previous studies (16,23) and again highlights the importance of events early in systole.

There are important limitations to our study that should be considered. There was some loss to follow-up of a relatively small number of patients. EF1 was measured by two trained observers retrospectively. Patients with a suboptimal echo image in which neither EF1 nor EF could be measured with confidence were excluded from the study. Measurements made in clinical use may exhibit more variability, although this will be reduced by improvements in imaging technology that will allow automatic determination of EF1. We compared EF1 with 2D rather than 3D GLS and 3D GLS is a better predictor of events in AS than 2D GLS (24). Some of the outcomes in our study may be dependent on the specific characteristics of our cohort and prospective replication in other cohorts will be required before the measurement can be reliably used to inform clinical management. Circulating biochemical biomarkers such as brain natriuretic peptide (BNP), have also been shown to predict events in asymptomatic AS (25,26) but may lack specificity. Further prospective studies will be required to determine the place of EF1 relative to other biomarkers in the risk stratification of AS, particularly in the various sub-groups of AS and to determine the importance of concurrent coronary artery disease.

In conclusion, EF1 is a simple robust measure of early systolic function, predicting major events in patients with asymptomatic AS and preserved EF. If the findings of the present study are replicated in other cohorts, it could be used to inform clinical management

of AS. It may also be useful for identifying early systolic dysfunction in other conditions where progression to late systolic function is associated with a poor prognosis.

Perspectives

Competency in medical knowledge

In patients with AS, a reduction in EF is associated with a poor prognosis and is a strong indication for intervention. Mechanosensing within myocytes may, however, act to preserve EF so that a fall in EF is a late event in the evolution of systolic dysfunction. EF1 is a novel measure of early systolic function that may be more sensitive than EF in detecting systolic dysfunction.

Translational Outlook 1

The present study is the first to demonstrate the independent prognostic value of EF1 in asymptomatic patients with preserved EF and moderate or severe AS. EF1 was superior to other measures of LV or aortic valve function. If confirmed in other cohorts EF1 could be used as a marker of increased risk to aid decision on prophylactic surgery in asymptomatic severe AS.

Translational Outlook 2

In patients with moderate AS a reduced EF1 appears to identify a high-risk group and it is possible that these should be offered further investigation for coronary disease or treatment of other determinants of LV dysfunction for example systemic hypertension. This may help us to better manage LV dysfunction beginning despite only moderate AS and may also improve LV recovery when aortic valve intervention is judged to be indicated. Patients with discordant velocity/gradient and AVA measurements are hard to classify and manage. Our preliminary results suggest that EF1 better classifies these than conventional measures, notably SVi.

Translational Outlook 3

The present study provides proof-of-concept for early systolic function as an important risk factor in other conditions that may be characterised by progression from early systolic to late systolic dysfunction.

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Figure legends

Figure 1. Measurement of EF1

Left ventricular volume measured from echo apical views and aortic valve (AV) flow measured from apical 5-chamber view using continuous wave Doppler. First-phase ejection fraction (EF1) was defined as percentage change in volume change from end-diastole (EDV) to volume (V1) occurring at time of peak aortic valve flow. EDV and V1 were obtained by Simpson's rule (see text for details). In this figure the entire time-varying LV volume curve is displayed to illustrate concept of EF1 (via a wall-tracking analysis performed in a single case).

Figure 2. Study population flow chart

218 out of 333 asymptomatic patients with moderate to severe aortic stenosis were included in the final analysis.

Figure 3. Receiver-Operating Characteristic (ROC) curve analysis

Receiver-Operating Characteristic (ROC) curve analysis for prediction of events at 2-year follow up in the total population. EF, ejection fraction; GLS, global longitudinal strain; MPG, mean pressure gradient; AVAi, aortic valve area index; SVi, stroke volume index; TAFR, trans aortic flow rate.

Figure 4. Kaplan-Meier curves according to EF1

Kaplan-Meier event-free survival curves according to EF1 (cut off value 25%) for a) total population (n=218); b) patients with moderate AS (n=73); c) patients with severe AS (n=49) and d) discordant AS (mean pressure gradient < 40mmHg and aortic valve area <1.0cm^2 , n=96).

Figure 5. Kaplan-Meier curves according to GLS, SVi and TAFR

Kaplan-Meier event-free survival curves according to a) Global longitudinal strain (GLS), b) stroke volume index (SVi) and c) trans-aortic flow rate (TAFR) in the discordant group (mean pressure gradient < 40mmHg and aortic valve area <1.0cm^2).

Figure 6. Kaplan-Meier curves for all-cause mortality

Kaplan-Meier curves for all-cause mortality for the total population: a) EF1 and b) GLS.

Table 1. Baseline patient characteristics and echocardiographic measures for the total population according to severity of aortic stenosis.

	Events (n=35)	No Events (n=38)	P	Events (n=44)	No Events (n=5)	P	Events (n=64)	No Events (n=32)	P
	Moderate (n=73)			**Severe (n=49)**			**Discordant (n=96)**		
Age (years)	68.6±12.3	63.4±17.1	0.142	69.2±12.4	69.7±5.0	0.936	69.3±13.2	72.8±12.9	0.215
Male Sex (%)	77.1%	57.9%	0.080	40.9%	40.0%	0.969	50.0%	50.0%	1.000
BMI (kg/m^2)	30.0±6.1	28.0±3.7	0.100	27.4±5.2	25.7±3.3	0.486	27.9±4.7	27.2±4.6	0.508
Heart rate (bpm)	69±15	72±13	0.347	73±13	66±5	0.255	70±12	65±10	**0.036**
SBP (mmHg)	144±16	136±20	**0.041**	140±24	140±29	0.975	136±24	130±15	0.206
DBP (mmHg)	76±11	75±11	0.566	73±10	77±22	0.430	71±11	70±10	0.490
Risk Factors									
Smoking (%)	31.4%	26.3%	0.630	34.1%	40.0%	0.793	39.1%	31.2%	0.453
Hypertension (%)	94.3%	81.6%	0.099	79.5%	80.0%	0.981	76.6%	62.5%	0.149
DM (%)	22.9%	21.1%	0.852	22.7%	0.0%	0.232	17.2%	15.6%	0.846
CAD (%)	65.7%	21.1%	**<0.001**	43.2%	40.0%	0.892	34.3%	37.5%	0.763
CKD (%)	28.6%	0.05%	**0.007**	18.2%	0.0%	0.297	32.8%	40.6%	0.451
Medications									
ACE/ARB (%)	25.7%	39.5%	0.211	15.9%	0.0%	0.335	20.3%	25.0%	0.600
Betablocker (%)	31.4%	23.7%	0.459	22.7%	20.0%	0.890	14.1%	18.8%	0.551
CCB (%)	28.5%	13.2%	0.103	36.4%	20.0%	0.466	18.8%	25.0%	0.477
Diuretic (%)	34.3%	21.1%	0.205	34.1%	20.0%	0.524	23.4%	14.3%	0.374
Statins (%)	65.7%	63.2%	0.820	70.5%	100%	0.156	56.3%	56.3%	1.000
Aspirin (%)	40.0%	31.6%	0.453	40.9%	40.0%	0.969	29.7%	34.3%	0.640
Echocardiography									
MPG (mmHg)	27.1±6.3	24.2±5.5	**0.041**	49.1±11.0	46.9±6.3	0.654	28.6±6.1	27.4±5.8	0.353
AVA (cm^2)	1.23±0.22	1.28±0.30	0.439	0.84±0.27	0.77±0.18	0.593	0.79±0.13	0.80±0.16	0.822
AVAi (cm2/m2)	0.63±0.12	0.69±0.15	**0.043**	0.44±0.13	0.45±0.09	0.891	0.43±0.09	0.44±0.09	0.813
EDV (ml)	100.3±29.9	103.5±30.8	0.651	99.5±38.5	91.2±48.3	0.658	87.1±32.3	86.7±31.0	0.955
SVi (ml/m^2)	32.9±8.9	37.3±9.4	**0.046**	32.8±10.7	36.9±18.9	0.453	30.0±10.0	30.9±9.6	0.643
SVi-VTI (ml/m^2)	46.1±10.5	47.0±10.7	0.729	42.4±10.8	45.9±8.3	0.487	33.8±7.5	33.7±6.7	0.923
LVMi (g/m2)	104.3±24.8	98.9±25.7	0.362	120.2±42.9	112.8±37.4	0.712	97.3±37.1	93.3±32.2	0.604
EF (%)	65.9±7.8	68.0±8.0	0.253	63.4±8.6	68.2±4.2	0.225	64.2±8.3	66.1±8.05	0.268
EF1 (%)	26.0±9.6	35.2±6.1	**<0.001**	23.5±11.6	36.2±5.2	**0.021**	25.1±10.1	33.1±5.0	**<0.001**
GLS (%)	-15.5±3.7	-18.2±4.5	**0.007**	-15.0±4.6	-15.8±1.9	0.700	-15.9±5.1	-17.4±3.1	0.125
S wave (cm/s)	8.1±2.4	8.4±2.0	0.518	7.4±2.0	8.8±2.6	0.151	7.7±1.8	7.9±1.7	0.582
E/e'	11.0±4.1	11.3±4.8	0.777	12.4±4.0	8.4±2.3	**0.035**	12.0±6.8	10.4±5.2	0.261
LAVi (ml/m2)	33.2±12.3	29.6±8.7	0.162	36.1±15.2	31.5±10.8	0.520	31.7±13.6	30.7±13.1	0.716
TPAVF (ms)	125.4±25.3	124.3±23.2	0.838	145.4±24.6	130.0±23.4	0.189	132.2±24.9	134.8±20.2	0.619
TPAVF/ET	0.42±0.08	0.43±0.09	0.775	0.48±0.08	0.43±0.08	0.166	0.44±0.09	0.44±0.08	0.963

Values are mean±SD. P values are the difference between Events and no Events for each group.

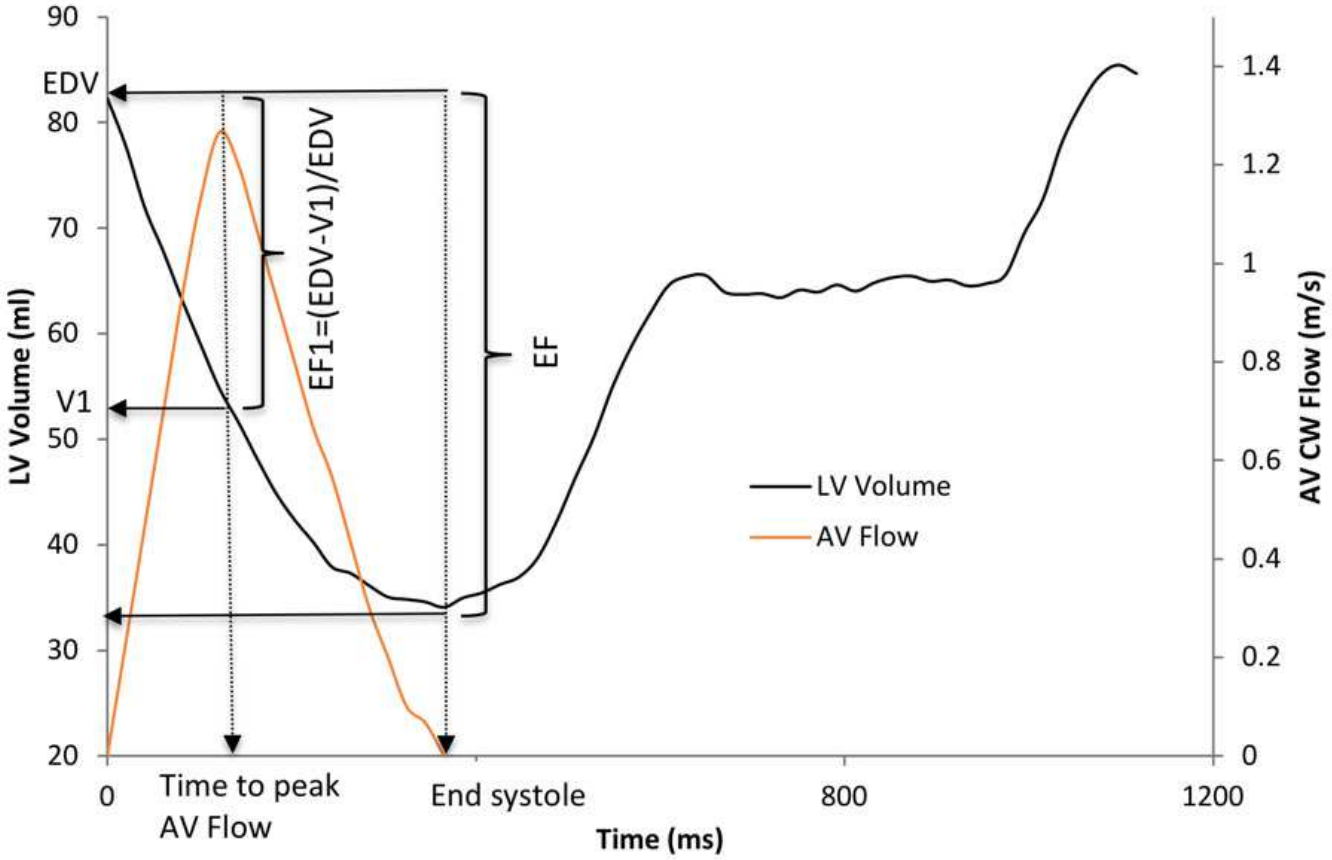
AS, aortic stenosis; BMI, body mass index; bpm: beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; DM, Diabetes Mellitus; CAD, coronary artery disease; CKD, chronic kidney disease; ACE, angiotensin-converting-enzyme; CCB, calcium-channel blocker; MPG, mean pressure gradient; AVA, aortic valve area; AVAi, aortic valve area index; EDV, end-diastolic volume; SVi, stroke volume indexed to body surface area; VTI: velocity time integral; LVMi, left ventricular mass index; EF, ejection fraction; EF1, first phase ejection fraction; GLS, global longitudinal strain; E/e', early mitral filling / tissue Doppler mitral annulus motion; LAVi, left atrial volume index; TPAVF, time to peak aortic valve flow; ET, ejection time.

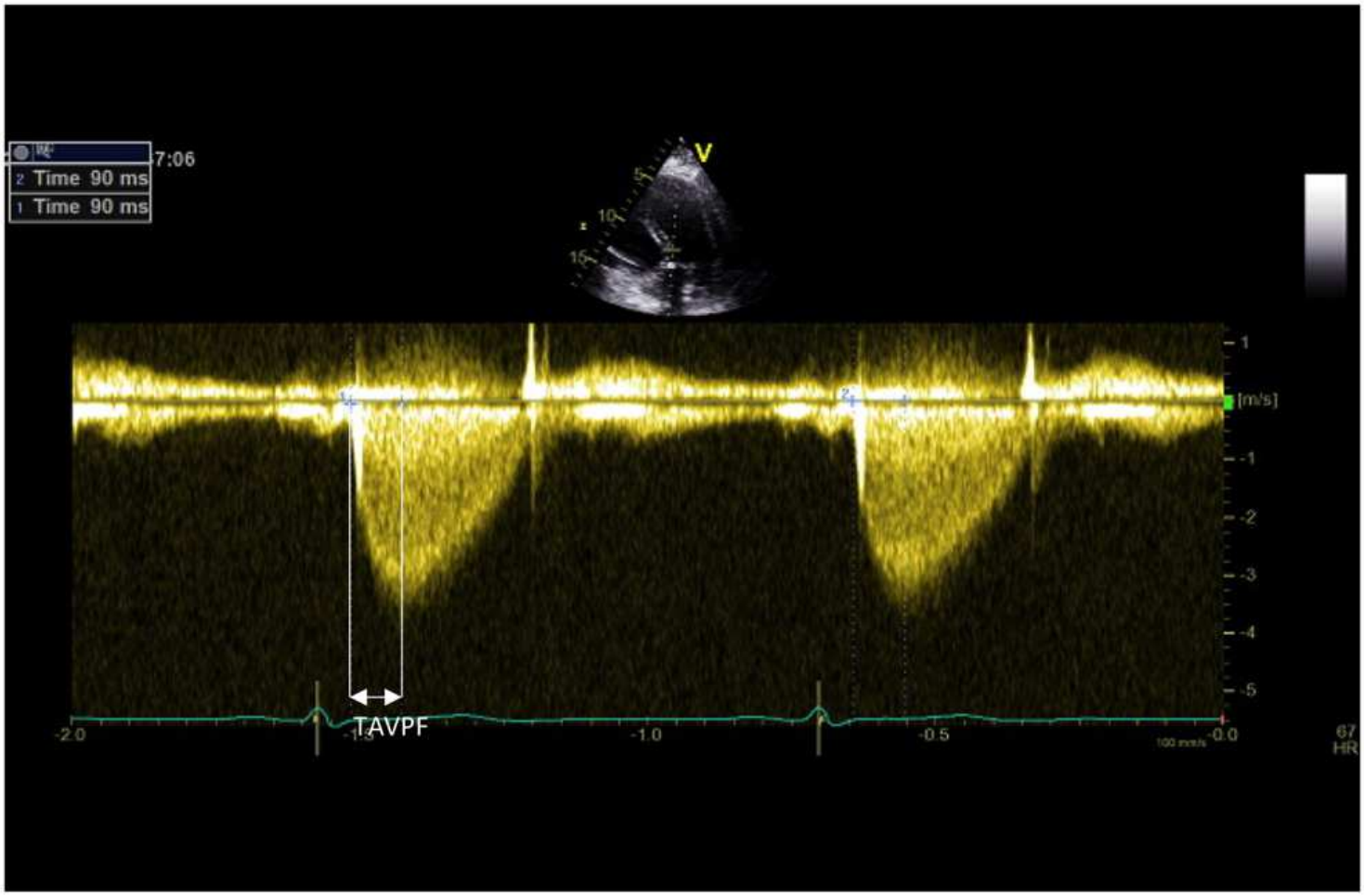
Table 2. Univariate and multivariate analysis of predictors of events

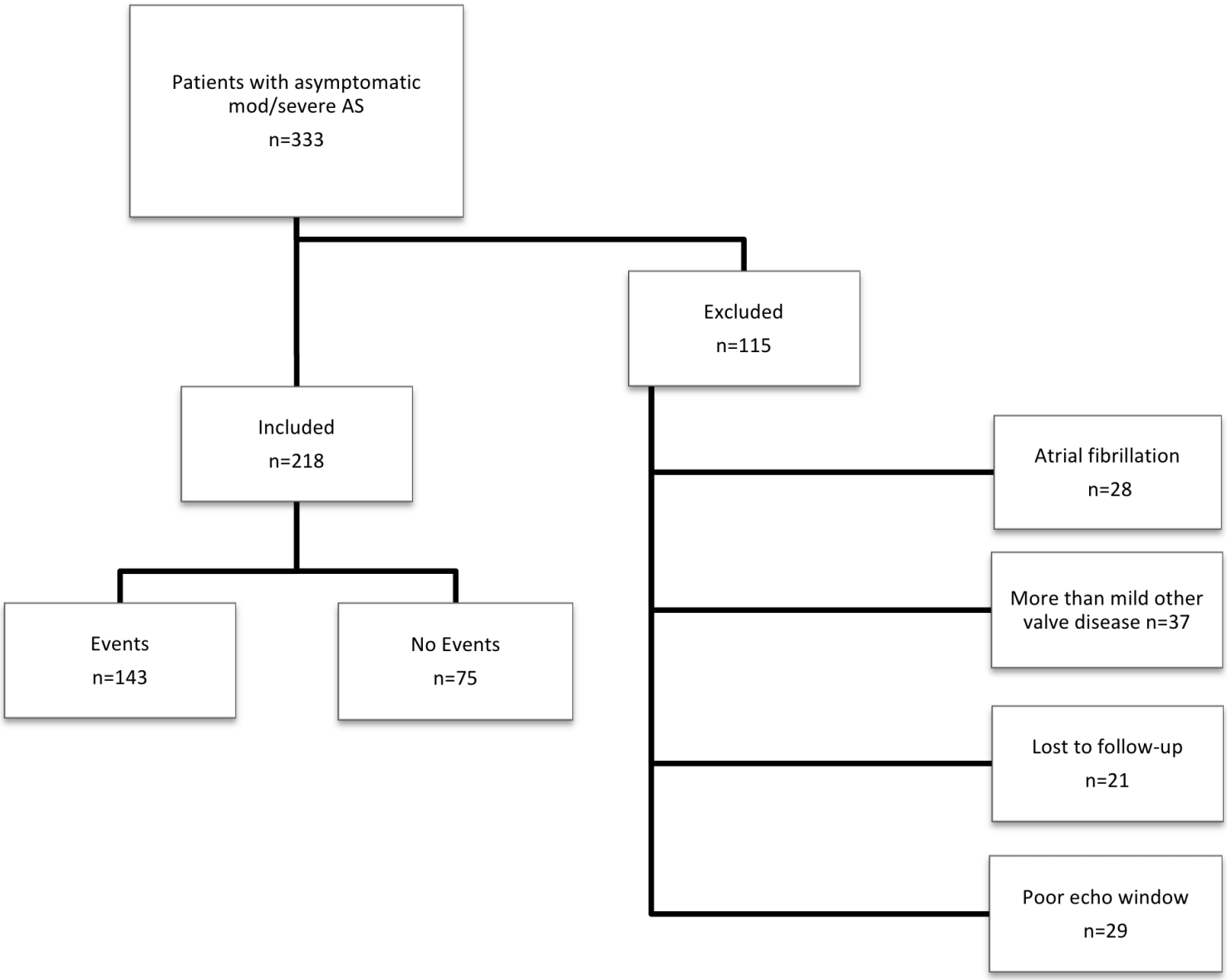
	HR	CI (95%)	P value	HR	CI (95%)	P value
	Total population (n=218)				**Discordant (n=96)**	
Univariate						
Age	1.011	0.999 – 1.023	0.061	0.868	0.981 – 1.016	0.868
Gender	0.883	0.631 – 1.235	0.466	0.909	0.555 – 1.490	0.705
BMI	1.023	0.988 – 1.059	0.199	1.017	0.966 – 1.071	0.515
Smoking	1.223	0.867 – 1.725	0.251	1.180	0.713 – 1.952	0.520
Hypertension	1.302	0.850 – 1.993	0.225	1.509	0.845 – 2.695	0.165
Diabetes	1.104	0.734 – 1.662	0.643	1.174	0.612 – 2.252	0.630
CAD	1.250	0.896 – 1.743	0.189	0.884	0.524 – 1.490	0.643
CKD	0.464	0.794 – 1.660	0.464	0.844	0.399 – 1.425	0.525
MPG	1.031	1.019 – 1.043	**<0.001**	1.008	0.968 – 1.050	0.709
AVAi	0.075	0.023 – 0.249	**<0.001**	0.193	0.013 – 2.924	0.236
LVMi	1.006	1.001 – 1.011	**0.022**	1.002	0.995 – 1.010	0.521
EF	0.962	0.941 – 0.983	**0.001**	0.966	0.936 – 0.997	**0.033**
Heart Rate	1.001	0.988 – 1.013	0.911	1.005	0.985 –1.027	0.615
Ejection time	1.002	0.997 – 1.007	**0.045**	1.000	0.992 – 1.008	0.970
SVi	0.974	0.957 – 0.992	**0.005**	0.985	0.957 – 1.013	0.298
TAFR	0.998	0.995 – 1.000	0.082	0.999	0.994 –1.003	0.576
GLS	1.091	1.046 – 1.137	**<0.001**	1.053	0.991 – 1.118	0.095
LAVi	1.023	1.009 – 1.036	**0.001**	1.013	0.994 – 1.032	0.195
TPAVF	1.007	1.000 – 1.014	**0.038**	0.707	0.986 – 1.010	**0.707**
TPAVF/ET	4.930	0.671 – 36.231	0.117	0.623	0.027 – 14.470	0.768
EF1	0.877	0.857 – 0.897	**<0.001**	0.901	0.872 – 0.931	**<0.001**
Multivariate Model 1						
LVMi	1.002	0.997 – 1.008	0.347	1.001	0.993 – 1.009	0.779
MPG	1.014	1.002 – 1.026	**0.022**	0.982	0.942 – 1.025	0.410

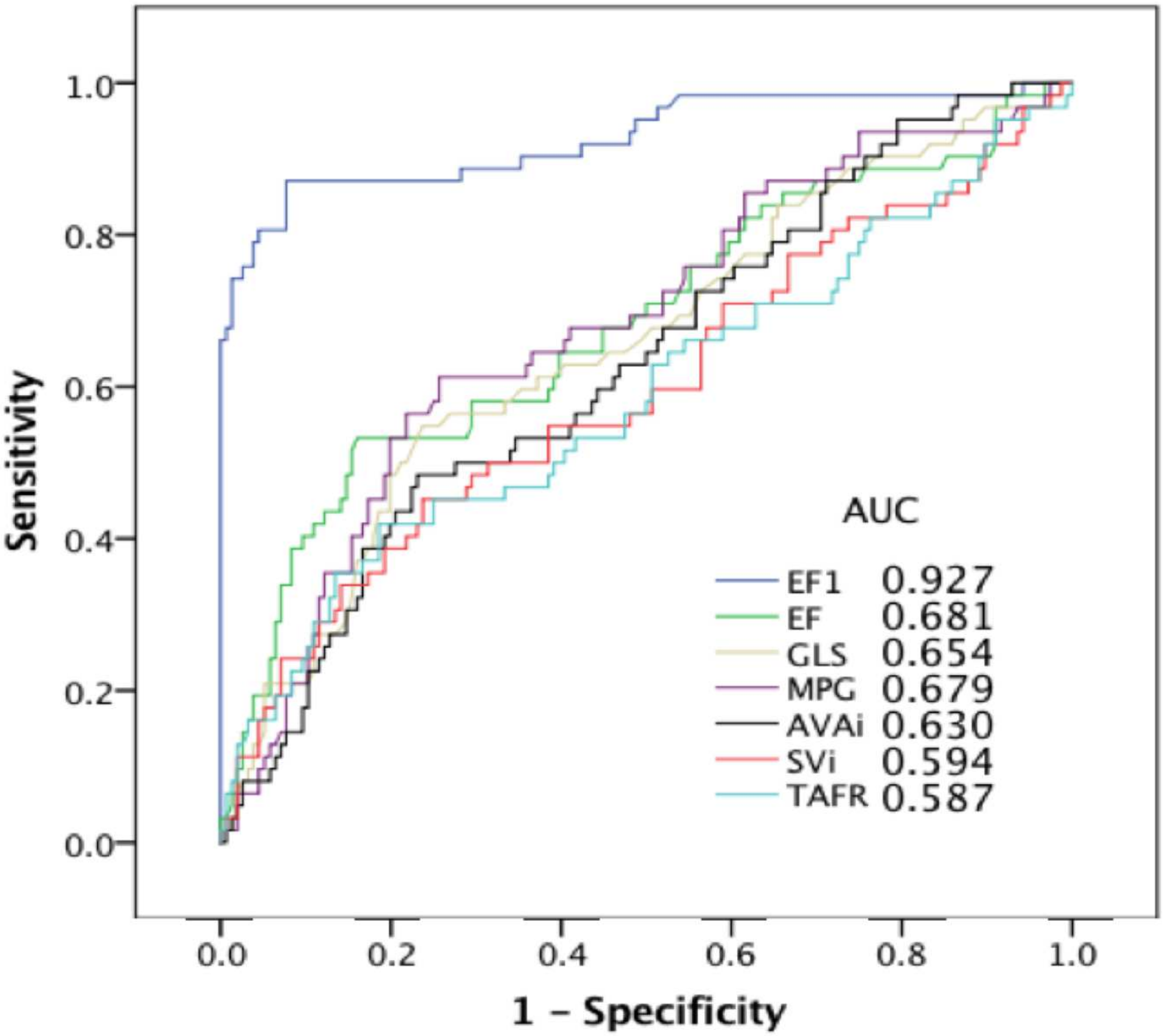
GLS	1.010	0.965 – 1.057	0.662	0.996	0.932 – 1.065	0.909
EF1	0.884	0.863 – 0.906	**<0.001**	0.897	0.866 – 0.930	**<0.001**
Multivariate Model 2						
MPG	1.008	0.994 – 1.022	0.249	–	–	–
AVAi	0.324	0.083 – 1.268	0.106	–	–	–
LVMi	1.005	0.999 – 1.011	0.092	–	–	–
EF	1.027	0.999 – 1.055	0.062	1.011	0.977 – 1.046	0.527
SVi	0.974	0.954 – 0.994	**0.012**	–	–	–
GLS	1.025	0.973 – 1.079	0.354	–	–	–
LAVi	1.013	0.998 – 1.028	0.094	–	–	–
TPAVF	0.693	0.994 – 1.009	0.693	–	–	–
EF1	0.885	0.863 – 0.903	**<0.001**	0.896	0.865 – 0.930	**<0.001**

AS, aortic stenosis; HR, hazard ratio; CI, confidence interval; BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; AV, aortic valve; MPG, mean pressure gradient; AVAi, aortic valve area index; LVMi, left ventricular mass index; EF, ejection fraction; SVi, stroke volume indexed to body surface area; TAFR: trans-aortic flow rate; GLS, global longitudinal strain; LAVi, left atrial volume index; TPAVF: time to peak aortic flow; ET: ejection time; EF1, first phase ejection fraction.

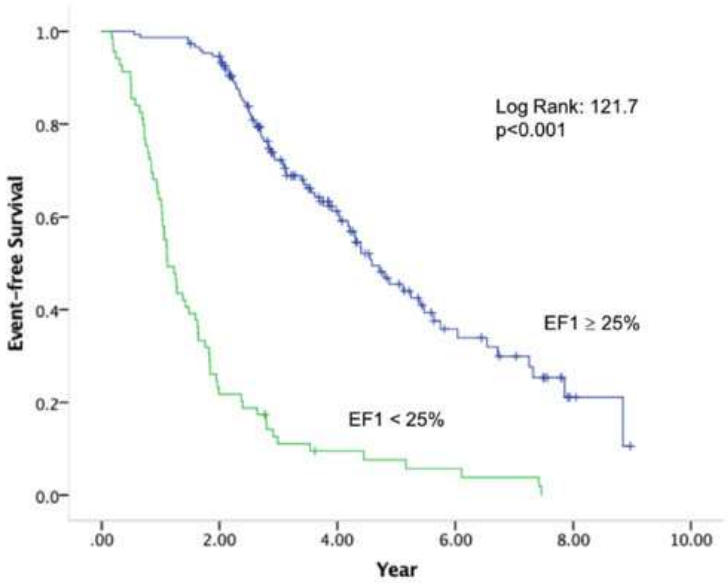

90
EDV
80
70
60
V1
50
40
30
20
LV Volume (ml)
EF1=(EDV-V1)/EDV
EF
LV Volume
AV Flow
1.4
1.2
1
0.8
0.6
0.4
0.2
0
AV CW Flow (m/s)
0
Time to peak
AV Flow
End systole
800
1200
Time (ms)


7:06
2 Time 90 ms
1 Time 90 ms
V
[m/s]
TAVPF
-2.0
-1.5
-1.0
-0.5
-0.0
67
HR


Patients with asymptomatic mod/severe AS
n=333
Excluded
n=115
Included
n=218
Atrial fibrillation
n=28
More than mild other valve disease n=37
Lost to follow-up
n=21
Poor echo window
n=29
Events
n=143
No Events
n=75

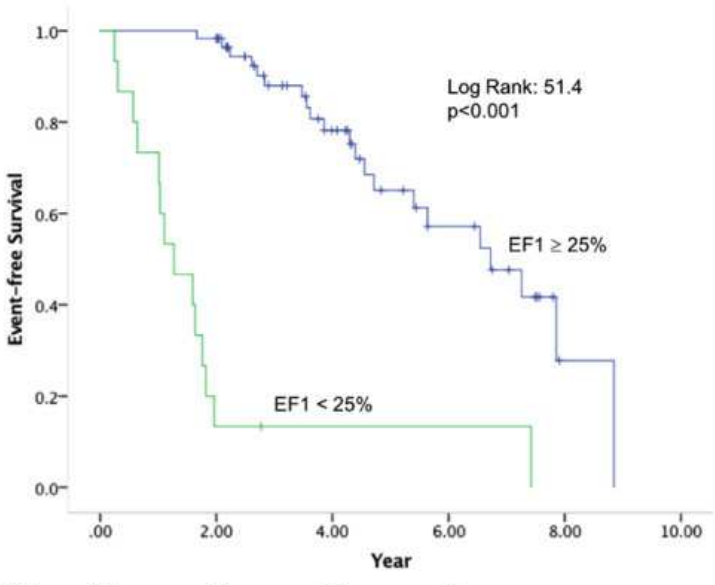

Sensitivity
1.0
0.8
0.6
0.4
0.2
0.0
0.0
0.2
0.4
0.6
0.8
1.0
1 – Specificity
AUC
EF1 0.927
EF 0.681
GLS 0.654
MPG 0.679
AVAi 0.630
SVi 0.594
TAFR 0.587

a)



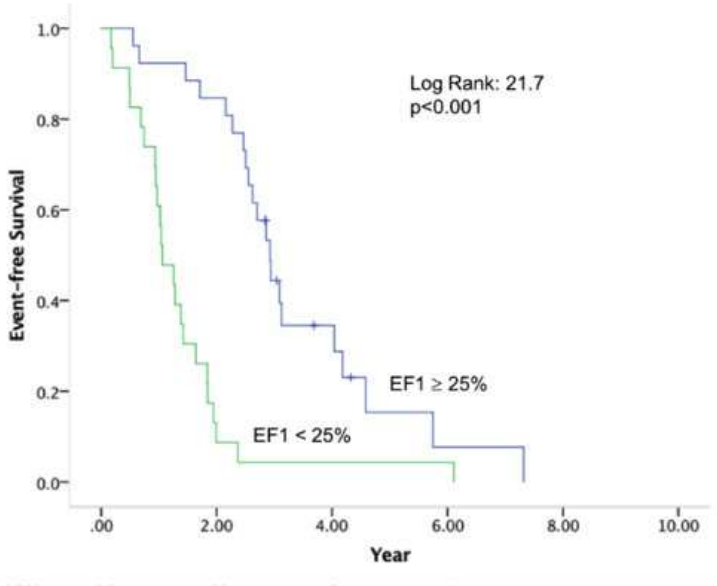
EF1≥25%	149	139	57	19
EF1<25%	69	15	5	3

b)



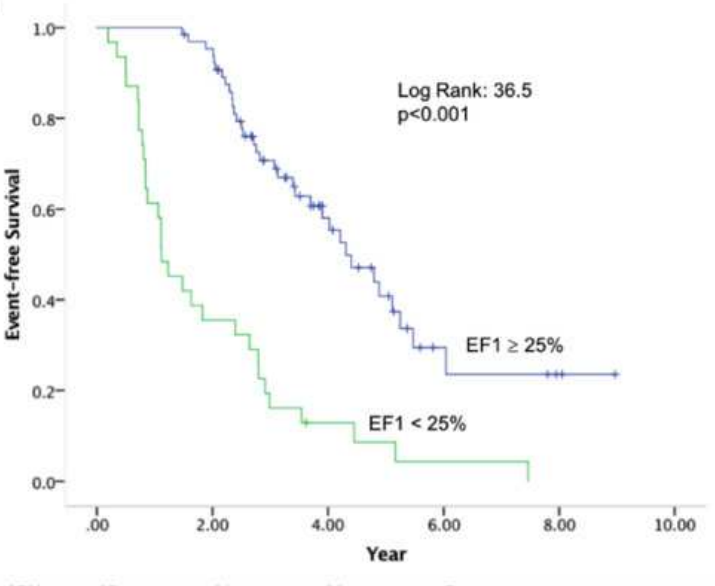
EF1≥25%	58	56	29	13
EF1<25%	15	2	1	1

c)



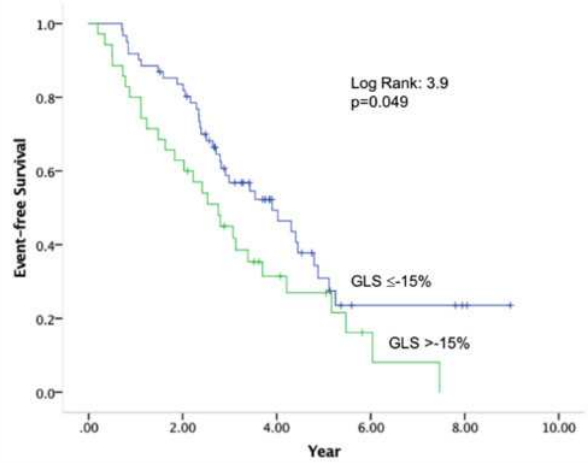
EF1≥25%	26	22	6	1
EF1<25%	23	2	1	1

d)



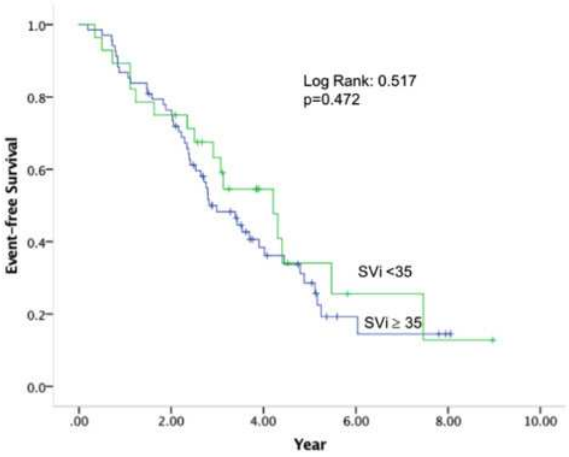
EF1≥25%	65	61	22	5
EF1<25%	31	11	3	1

a)



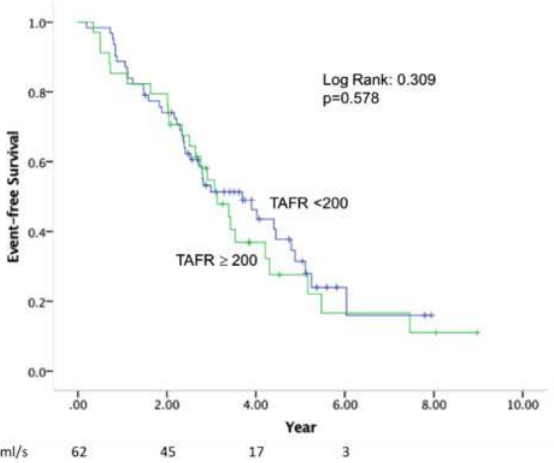
GLS≤-15%	61	50	17	4
GLS>-15%	35	22	8	2

b)



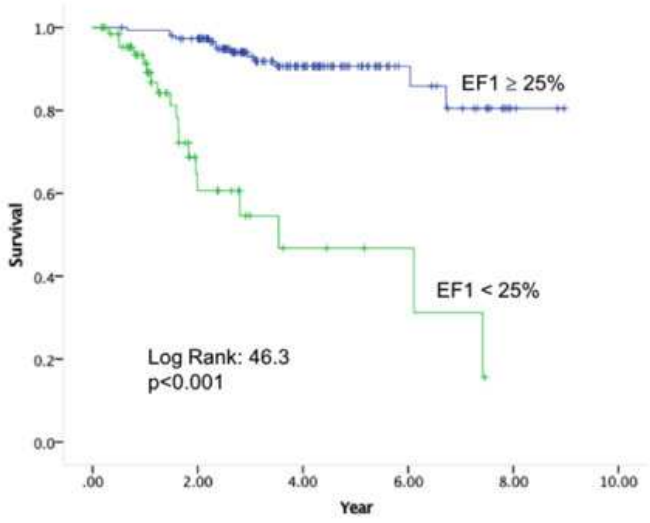
SVi≥35ml/m²	68	51	17	4
SVi<35ml/m²	28	21	8	2

c)



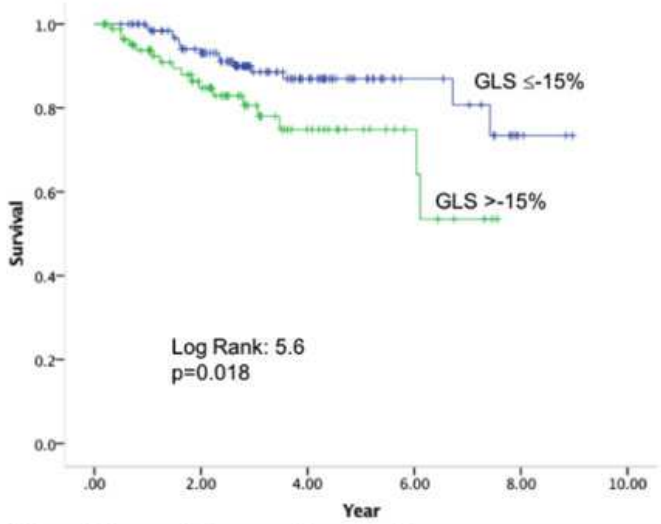
TAFR<200ml/s	62	45	17	3
TAFR≥200ml/s	34	27	8	3

a)



EF1≥25%	149	139	57	19
EF1<25%	69	15	5	3

b)



GLS≤-15%	131	102	43	15
GLS>-15%	87	52	19	7