Effect of the 2017 European Guidelines on Reclassification of Severe Aortic Stenosis and Its Influence on Management Decisions for Initially Asymptomatic Aortic Stenosis

Chan, Daniel C. S.; Singh, Anvesha ; Greenwood, John P.; Dawson, Dana K.; Lang, Chim C.; Berry, Colin

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Title

Effect of the 2017 European guidelines on re-classification of severe AS and its influence on management decisions for initially asymptomatic Aortic Stenosis

Authors

*Daniel C.S. Chan, BMBS, PhD[1]; *Anvesha Singh, MBChB, PhD[1]; John P. Greenwood, MBChB, PhD[2]; Dana K. Dawson, DM, PhD[3]; Chim C. Lang, MBChB, MD[4]; Colin Berry, MBChB, PhD[5]; Mini Pakkal, MBBS, MD[6]; Russell J. Everett, MBChB, BMedSci[7], Marc R. Dweck, MBChB, PhD[7], Leong L. Ng, MB BChir, MD[1], Gerry P. McCann, MBChB, MD[1]

*authors made equal contribution to the manuscript.

Short Title

Reclassification of severe asymptomatic AS

Affiliation and Addresses of Authors

[1]Department of Cardiovascular Sciences, University of Leicester and Cardiovascular Theme, NIHR Leicester Biomedical Research Centre, Glenfield Hospital, Groby road, Leicester, LE3 9QP, UK; [2]Multidisciplinary Cardiovascular Research Centre & The Division of Biomedical Imaging, Leeds Institute of Cardiovascular & Metabolic Medicine, Leeds University, Leeds, LS2 9JT, UK; [3]Cardiovascular Medicine Research Unit, School of Medicine and Dentistry, University of Aberdeen, Polwarth Building, Foresterhill, Aberdeen AB25 2ZD, UK; [4]Division of Molecular & Clinical Medicine, Ninewells Hospital and Medical School, Dundee DD1 9SY, UK; [5]BHF Glasgow Cardiovascular Research Centre, University of Glasgow, 126 University Place, Glasgow, G12 8TA, UK; [6]Toronto General Hospital, Department of Medical Imaging, 585 University Ave., Toronto, ON M5G 2N2 Canada; [7]BHF Centre for Cardiovascular Science, University of Edinburgh, Edinburgh, EH16 4SB, UK

Corresponding author: Dr Daniel Chan, Glenfield Hospital, Groby Road, Leicester LE3 9QP, UK. Telephone: 0116 2583038 Fax: 0116 2583422

Email: dcsc1@le.ac.uk

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Abstract

Background: The 2017 European Society of Cardiology guidelines for valvular heart disease included changes in the definition of severe aortic stenosis. We wanted to evaluate its influence on management decisions in asymptomatic patients with moderate-severe aortic stenosis.

Methods: We reclassified the aortic stenosis(AS) severity of the participants of the PRIMID-AS study, using the 2017 guidelines, determined their risk of reaching a clinical endpoint (valve replacement for symptoms, hospitalisation or cardiovascular death) and evaluated the prognostic value of aortic valve(AV) Calcium score and biomarkers. Patients underwent echocardiography, cardiac magnetic resonance imaging, exercise tolerance testing (ETT) and biomarker assessment.

Results: Of the 174 participants, 45% (56/124) classified as severe AS were reclassified as moderate AS. This Reclassified group was similar to the original moderate group in clinical characteristics, gradients, calcium scores and remodelling parameters. There were 47 primary endpoints (41 valve replacement, 1 death, 5 hospitalisations - 1 chest pain, 2 dyspnoea, 1 heart failure, 1 syncope) over 368±156 days follow-up. The severe and Reclassified groups had higher risk compared to moderate group (adjusted hazard ratio 4.95 (2.02-12.13) and 2.78 (1.07-7.22) respectively), with the Reclassified group demonstrating an intermediate risk. A mean pressure gradient (MPG)≥31mmHg had a 7× higher risk of the primary endpoint in the Reclassified group. AV Calcium score was more prognostic in females and low valve area, but not after adjusting for gradients. NTproBNP and myocardial perfusion reserve were associated with the primary endpoint, but not after adjusting for positive ETT. Troponin was associated with cardiovascular death or unplanned hospitalisations.

Conclusions: Reclassification of asymptomatic severe AS into moderate AS was common using ESC 2017 guidelines. This group had an intermediate risk of reaching the primary endpoint. Exercise testing, multi-modality imaging and lower MPG threshold of 31mmHg may improve risk stratification.

Clinical Trial Registration Information: clinicaltrials.gov - NCT01658345

Keywords: aortic stenosis, aortic valve calcification, exercise tolerance test, calcium score

Clinical Perspective

Patients with aortic stenosis (AS) valve area< 1.0cm^2, low gradient (mean <40mmHg) and normal flow (>35ml/m^2) are now downgraded from severe to moderate AS in the 2017 European guidelines for valvular heart disease. We applied the new criteria to an initially asymptomatic cohort of moderate-severe AS patients to ascertain the extent of the reclassification. We found that 45% of patients previously classified as severe AS were downgraded to moderate AS. These reclassified patients had more than a 2.5 higher risk of progression to spontaneous symptoms, hospitalisation or death, compared to patients with moderate AS, but this risk was lower than patients with severe AS (high gradient or low gradient low flow). A mean pressure gradient ≥31mmHg identified reclassified patients at highest risk of progression to symptoms (7-fold higher relative risk). Exercise testing remained a useful independent predictor of symptom progression in the new definition of severe AS, but not in the reclassified group. Therefore, with asymptomatic AS patients with low valve area but low gradients, clinicians should use an integrated approach with multiparametric assessment (Calcium score of aortic valve, Transesophageal echocardiography), and scrutinize the measurements carefully, recognizing that this cohort of patients are at elevated risk of progression, in particular if the mean pressure gradient is ≥31mmHg.

Introduction

The management of asymptomatic patients with severe aortic stenosis (AS) is controversial. Symptoms herald a malignant phase[1]. Arguably, aortic valve replacement (AVR) should occur before symptom onset or irreversible fibrosis, measurable on cardiovascular magnetic resonance imaging (CMR) as late gadolinium enhancement (LGE), if long-term outcomes are to be improved[2]. Natriuretic peptides and high-sensitivity troponin (HsTNI) help identify asymptomatic patients at risk, but high values also associate with higher perioperative risk[3] and post-operative outcome[4, 5]. Better tools to optimize surgical timing are urgently needed.

Both the 2012 European and 2014 American guidelines define AS in a similar way[6, 7]. However, the updated 2017 European guidelines places emphasis on pressure gradients (see Table-1). In low gradient (mean pressure gradient, MPG<40mmHg) AS with preserved ejection fraction (EF), an integrated approach, including aortic valve calcium score (AV-calcium score) assessment by multi-detector computed tomography (MDCT), is suggested[8]. Thus, low gradient severe AS is reclassified as moderate AS, apart from low flow status (stroke volume index, SVI≤35ml/m^2) with high calcium scores, which remain as severe AS. Whether this new classification improves risk stratification and identification of those who would benefit from AVR in initially asymptomatic patients is unknown.

The aims of this study were: (i) to use the updated European 2017 guidelines to reclassify patients in the 'Prognostic Importance of Microvascular Dysfunction in asymptomatic patients with AS' (PRIMID-AS) study[9], previously defined as severe AS based on the European 2012 guidelines; (ii) to ascertain whether the re-classification, troponin, natriuretic peptides or exercise testing (ETT) can help guide management decisions and (iii) to evaluate the additive prognostic value of AV-Calcium scores.

Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

The PRIMID-AS study was a prospective, observational, multi-centre study of asymptomatic moderate to severe AS in the UK, comparing myocardial perfusion reserve (MPR) with exercise tolerance test (ETT)[9, 10]. Briefly, inclusion criteria were ≥2 of: aortic valve area (AVA)<1.5cm^2, peak gradient >36mmHg or MPG>25mmHg, and willingness to accept AVR if symptoms developed. Exclusion criteria were: previous coronary artery bypass grafting or valve surgery, absolute contraindications to CMR or adenosine, other severe valve disease, EF≤40%, recent myocardial infarction (<6 months), persistent atrial fibrillation and planned surgery. All participants provided written informed consent. The study had National Research Ethics Service approval and complied with the Declaration of Helsinki.

Investigations

All patients underwent transthoracic echocardiography, AV-Calcium scoring, symptom-limited bicycle ETT, venous blood sampling for biomarker analysis and 3T multi-parametric CMR (including stress and rest first-pass perfusion imaging, pre- and post-contrast T1 mapping and LGE), as previously published[9, 10]. For the purposes of this paper, a positive ETT was defined according to the 2017 European guidance: 'any AS symptom on exercise testing or fall in BP below baseline during exercise'[8]. Core lab CMR image analysis was undertaken by a single blinded observer (AS). SVI was calculated on echocardiography as the product of the left ventricular outflow tract area and its velocity time integral and indexed to body surface area[11, 12]. MDCT images through the AV were acquired in the diastolic phase of the cardiac cycle, using sequential acquisitions of 3mm slices in full inspiration. AV-calcium score was calculated using the Agatston method[13].

Biomarker Analysis

Plasma was processed within 4 hours of venepuncture and stored at -80°C. Biomarker batch analysis was performed at the end of the study. N-Terminal pro-Brain Natriuretic Peptide (NTproBNP) was analysed using our in-house non-competitive immunoassay[14]. HsTNI was analysed using the ARCHITECT *STAT* high-sensitivity assay (Abbott Laboratories, Abbott Park, Il, USA).

Follow-up and endpoints

Patients had a minimum follow-up of 12 months or until reaching the primary endpoint. The primary endpoint was a composite of AVR for spontaneous symptoms or hospitalisation with heart failure, chest pain, syncope or cardiovascular death. Endpoints were adjudicated by 2 independent cardiologists. Management decisions were left to the attending physicians. The results of all research tests were kept blinded from the clinical teams, to avoid the results biasing the decision-making. ETT was deliberately not used to define symptom status in this study, as exercise-induced symptoms was considered a class IIB(C) indication in the American guidelines at the time of the study design[15], and it was not routinely used in our institution. More importantly, the aim of the original study was to compare ETT to MPR in predicting outcomes and spontaneous symptom onset.

Definitions

The differences between the 2012 and 2017 European guidelines are shown in Table-1. Using the new definitions, 3 groups emerged: “Moderate” (moderate by both criteria); “Reclassified” (severe by 2012 but moderate by 2017 criteria); and “Severe” (severe by both criteria). Those with low gradient severe AS were reclassified as moderate if they had normal flow, or low flow with low AV calcium scores as shown in Table-1. Sex-adjusted AV-Calcium score (AVCalcIndex) was calculated by dividing the calcium score by the cut-off for the sex (2000/1200AU for males/females).

Statistical Analyses

Normality was assessed using Kolmogorov-Smirnoff tests, histograms and Q-Q plots. Parametric data are expressed as mean±standard deviation. Non-parametric data are expressed as median [25th, 75th centile]. Discrete variables are presented as number (%). Continuous variables were compared between groups with the one-way ANOVA or Kruskal-Wallis test as appropriate. A Bonferroni correction was applied for post-hoc comparisons. The χ^2 test or Fisher’s exact test was used for categorical variables. Where appropriate, variables were Log_2-transformed for modelling purposes. AV Calcium scores were transformed with Log_n(AV Calcium score+1) to accommodate zero-calcium scores for modelling. Cox regression analyses were performed to ascertain hazard ratios (HR) of reaching the endpoint, and expressed as HR (95% Confidence Interval,CI). Binary variables were modelled as continuous

variables. Non-binary categorical variables were modelled as categorical variables to the reference group. For Cox and Fine-Gray multivariable analyses, variables of interest were adjusted for confounding covariates previously known to be associated with the end-point, with limited number of covariates to avoid overfitting. Collinearity of covariates in models was assessed by calculating the variance inflation factor, and values >2.5 were considered collinear. With collinear variables, only the most significant collinear covariate in univariate association (by p-value) was used in any model. The assumption of linearity was assessed by plotting Martingale residuals against continuous variables to ensure the correct functional form was used. Proportional hazards assumption was tested using statistics and graphs based on the Schoenfeld residuals. Where competing events were important confounders (e.g. surgery preventing hospitalisation or death), Fine-Gray regression for competing events was performed. Kaplan-Meier curves were constructed to display differences in probability of event-free follow-up and the log-rank test applied. The Holm method was used for post-hoc comparisons of Kaplan-Meier curves[16]. All analyses were performed in Rver3.1.3[17] with the 'Rcmdr' package[18] and utilising the 'Rcmdrplugin.EZR' plugin[19]. A two-tailed p-value < 0.05 was taken as statistically significant.

Results

174 patients were recruited and followed up for an average of 369±156 days (range 181-791). Using 2012 criteria, 71.3% (124/174) had severe AS compared to only 39.1% (68/174) using 2017 criteria (Figure 1). Therefore, 56 patients (32% of total and 45% of those originally classified as severe) were reclassified from severe to moderate ('Reclassified' group).

Baseline Characteristics

The baseline demographic of the three groups (Moderate, Reclassified and Severe) were similar, with the greatest proportion of positive ETT in the reclassified group, though this was not statistically significant (Table-2). The characteristics for severe and moderate AS using 2012 and 2017 definitions are shown in Table S1.

Echocardiography and CT

All patients in the Reclassified group had AVA index (AVAI)<0.6cm^2, but 44.6% had AVA>1cm^2. As expected, the Reclassified group had valve areas similar to the Severe group, but gradients similar to the Moderate group, with significantly lower SVI than both groups.

Calcium scores in the Reclassified group were similar to the Moderate group and significantly lower in both than the severe group (Table-2). Although there was correlation between AVCalcIndex and AVA, AV-Vmax and MPG, scores could be low even with high MPG, AV-Vmax or low AVA (Figure S1).

CMR

In keeping with gradient differences, LV remodelling in the Reclassified group was of similar magnitude to the Moderate group, with mass/volume and LV mass index being significantly lower in both compared to the Severe group (Table-2). The MPR was significantly higher in the Reclassified and Moderate groups compared to the Severe group. There were no significant differences in LGE or extracellular volume fraction (ECV) and the indexed extracellular volume (iECV) between groups.

Biomarkers

There was a progressive increase in HsTNI values with increasing AS severity, with the levels in the Severe group being statistically higher than the other groups. There was no significant difference in the NTproBNP levels between groups.

Primary Endpoint

There were 47 (27%) primary endpoints (Table-2): 41 AVR for spontaneous symptoms, 1 cardiovascular death & 5 hospitalisations (1 chest pain, 2 dyspnoea, 1 heart failure, 1 syncope) (Figure S2). The Kaplan-Meier curve for event-free survival comparing the three subgroups, showed incrementally worse outcome from moderate to Reclassified to severe groups (Figure-2). Separate Kaplan-Meier curves using the 2012 and 2017 criteria are shown in Figure S3. Univariate associations (unadjusted and adjusted) with the primary endpoint are presented in Table S2 and Table-3. Cox models showed that both the Reclassified and severe group had a significantly higher risk of reaching an endpoint (2.78× and 4.95× respectively), compared to the moderate group (when modelled as

categorical groups). However, after adjusting for a positive ETT, the Reclassified group became not significant (p=0.051).

Although estimated glomerular filtration rate (eGFR), NTproBNP and MPR were significantly associated with the primary endpoint on univariate analysis (Table S2), none were significant after adjusting for sex, ETT and severe AS (2017 definition) (Table S3). HsTNI was not associated with the primary endpoint, but was associated with cardiovascular death or unplanned hospitalisation, in competing events proportional hazards regression, even after adjusting for age, MPG or AVA and ETT (Table S4).

Value of Calcium Scores

Log-transformed calcium scores were not associated with the primary endpoint in cox models, although after adjusting for sex, this was significant (Table S2 and S3). Likewise, AVCalcIndex was associated with the end-point on univariate analyses. Unadjusted subgroup analyses suggest that AVCalcIndex was prognostic in females, AVA≤1cm^2, AVAI≤0.6cm^2/m^2 and patients with positive ETT, although p-interaction was only significant for valve areas. However it was not statistically significant after adjusting for AV-Vmax (Figure 3).

Further risk stratification within the Reclassified group

Univariate associates with primary endpoint in the Reclassified group are shown in Table-4. In this group, only MPG was significantly associated with the primary endpoint, whilst sex, ETT, fibrosis, remodelling markers and biomarkers were not. A receiver operating curve identified 31mmHg as an ideal cut-off value with the highest combined sensitivity and specificity for dichotomising risk (Figure S4). Kaplan Meier analyses using a ≥31mmHg cut-off and 5mmHg interval cut-offs between 20-40mmHg (Figure 4) further demonstrate this.

Hazard ratios of accepted dichotomized markers of AS severity and the more novel MPG≥31mmHg marker found in this cohort was compared (Table S5). MPG≥31mmHg had numerically the largest hazard ratio as well as the highest c-statistic, indicating better model fit.

Discussion

In this manuscript, we use the 2017 European guidelines to re-classify AS severity in a well-characterised cohort of asymptomatic patients with at least moderate AS, and assess the clinical characteristics and outcome of this new Reclassified group. Nearly half the participants (56/124) were downgraded from severe to moderate AS. There were key differences in this Reclassified group compared to both previously defined moderate and severe groups. The Reclassified group demonstrated an intermediate risk of developing a primary endpoint (mainly driven by spontaneous symptom onset), with intermediate troponin levels. Patients in the Reclassified group with MPG≥31 mmHg were at ~7 times higher risk of primary endpoints; and may be a better marker of risk in this cohort compared to other markers of severe AS, which could be useful to clinicians in risk-stratifying within this intermediate risk group.

Characteristics of reclassified patients

The Reclassified group is a heterogenous group; all with low gradients, but some with low flow and less calcification, whilst others had normal flow but more calcification. As expected from the definition, the Reclassified group had gradients closer to the moderate group and AVA similar to severe, but with the lowest SVI. However, their cardiac remodelling pattern was closer to the moderate group. There was a non-significant trend to increasing proportions of patients with LGE, from moderate to Reclassified to severe groups, a feature of poor prognosis in AS[20, 21]. HsTNI was also incrementally elevated in those respective groups although the difference between the moderate and Reclassified group was insignificant. HsTNI has been shown to be associated with LGE and poor prognosis in AS[4].

Assessing AS severity

In AS, we classify patients as having moderate or severe disease to aid clinical decision making. However, there is no single ‘number’ that should define ‘severe AS’. Experts generally agree that severe AS is associated with a poorer outcome[22]. AV-Vmax>4m/s is associated with a much higher risk of progressing to AVR or death[23, 24]. Moderate AS is also associated with an increased event rate, with a hazard ratio of 1.6 when comparing AV-Vmax≥3m/s vs <3m/s[25], whilst AVAI<0.6cm^2/m^2 is associated with a doubling of the risk[26]. The markers of AS severity can be discordant and present

clinicians with a 'difficult' decision making process[27]. The change in the criteria to define severe AS in the 2017 European guidelines reflects the uncertainty regarding the low gradient group with a low AVA. The updated guidance recognizes the increased risk in those with low flow with preserved EF[11], but classifies the group with normal flow as "likely moderate AS". Some of the low-flow group with lower AV calcification will also be reclassified as moderate AS.

Our findings of an 'intermediate' risk and HsTNI profile in this group may have important implications for these patients, where decision to refer for surgery may be deferred due to their AS being classified as 'moderate'. Whilst some have described a poorer prognosis in symptomatic patients with normal flow, low gradient, AVA<1cm^2 AS, with a significant survival benefit from AVR[28, 29], others found these patients to have the same prognosis as moderate aortic stenosis[30]. We found that in this present study, using MPG≥31mmHg appeared to dichotomise risk of spontaneous symptoms or events better than the accepted 40mmHg cut-off, or any other dichotomised marker of AS severity. This finding is consistent with the 2017 European guidelines[31] which mention that low gradient AS is more likely to be severe if MPG was between 30-40mmHg. This deserves more emphasis, as evidenced in this study, especially if the flow is normal, and could be helpful in identifying those who should be considered for AVR sooner.

Value of calcium scores

Calcium score corroborate AS severity[32] and valvular calcification on echocardiography is associated with worse outcomes in severe asymptomatic AS[33]. Sex-specific calcium score could accurately identify severe AS, and was independently associated with valve replacement or death[34], although exact cut-offs vary (2062/1377AU[34] *vs* 2065/1274AU[35] *vs* 2000/1200AU[8] in males/females respectively). Our derived cut-offs (2269/1146) were within this range (Figure S5). High calcium scores has been associated with increased mortality risk in all subgroups, including in non-severe AS[36], making it a useful 'arbiter' of AS severity, and this may be particularly true when the AVA is discordant with the gradients. We found calcium scores to be associated with the primary endpoint only in the low valve area subgroup, but not after adjusting for AV-Vmax, reinforcing that calcium scores are a lesser surrogate for gradients.

However, one could hypothesize that calcium scores were most valuable in females with low valve areas but discordant gradients.

CMR markers

The lack of difference in CMR markers of fibrosis between the groups was surprising, because LGE is associated with residual risk post-AVR[2]. Neither ECV nor LGE were associated with the primary endpoint in PRIMID-AS[10], which was primarily driven by spontaneous symptom onset, suggesting disparate mechanisms for symptom onset and fibrosis development, both of which lead to poor prognosis in AS. It is concerning that 42% of those with moderate AS already have LGE, rising to half of the severe group, similar to the findings of a recent meta-analysis showing LGE to be present in 49.6% of AS[37]. The increasing levels of HsTNI between the classes further corroborates the incremental fibrosis[4] and HsTNI was associated with cardiovascular death and unplanned hospitalisation even after adjusting for age, pressure gradients and a positive ETT. Development of symptoms is likely a complex and multifactorial process, with structural and functional remodelling playing a role, along with patient's comorbidities, deconditioning and metabolic factors. The mechanisms are likely similar to those that impair exercise capacity. MPR is an independent predictor of aerobic exercise capacity[38] and associated with outcome in the PRIMID study[10], whilst ECV was independently associated with MPR[39]. In this study, we showed MPR to be significantly lower in the severe group, corroborating its importance in exercise limitation and symptom onset.

Should surgery be offered earlier?

As surgery becomes safer and the less invasive transcatheter option more widespread, there should be a drive to identify patients for early intervention before irreversible remodelling occurs. There are now 4 trials (EVoLVeD, AVATAR, EARLY TAVR and EASY-AS) underway, testing an early intervention strategy in asymptomatic patients with severe AS (ClinicalTrials.gov NCT03094143, NCT02436655, NCT03042104, NCT04204915). Our data suggests the potential use of AVA<1.0cm^2, a higher calcium score or MPG≥31mmHg as selection criteria for earlier intervention in the intermediate group, given the higher risk of developing symptoms and events.

Strengths and Limitations

The PRIMID-AS study's main strengths were its prospective, multicentre design, run to clinical trial standards with blinded image analysis, independent trials unit data handling and blinding of physicians and patients to results of their research tests. Patients referred for surgery whilst asymptomatic were not included in the primary endpoint. Limitations were a low sample size, most events were driven by valve replacement, although we were particularly interested in spontaneous symptom onset as a marker of high risk; all participants had EF>40% and could perform an ETT, and were all asymptomatic at recruitment. As such, findings cannot be generalised to patients outside of these parameters.

Conclusions

The 2017 European guidelines downgraded severity in 45% of patients with severe AS when compared to 2012 criteria. The reclassified patients have an intermediate risk of reaching the primary endpoint, despite having similar gradients and remodelling characteristics as the moderate group, reinforcing the need for careful assessment in this group. Exercise testing, AV-calcium score and utilisation of lower thresholds of MPG≥31mmHg may aid risk stratification.

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Disclosures

None.

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Text Tables

Table 1: Differences in definition of severe AS with preserved systolic function between the guidelines

	Variables	ESC 2012[6]	ESC 2017[8]
		Any of A, B or C	Any of A or B
A	Vmax & MPG	Vmax > 4 m/s or MPG > 40 mmHg	Vmax ≥ 4 m/s or MPG > 40 mmHg
B	AVA	AVA < 1 cm^2	AVA ≤ 1 cm^2 *and* SVi ≤ 35 mL/m^2 *and* Integrated approach
C	AVAi	<0.6cm/m^2	-
	Notes	-	If AVA ≤ 1 cm^2 and SVi > 35 mL/m^2 *unlikely* to be severe AS, unless A or B satisfied

Integrated Approach (Criteria increasing likelihood of low-flow severe AS):-

Clinical Criteria	Typical Symptoms without other explanation Age >70
Qualitative imaging Data	Left ventricular hypertrophy not due to hypertension Reduced LV longitudinal function without other explanation
Quantitative imaging Data	- MPG 30-40mmHg - AVA ≤0.8cm^2 - Low flow (SVi < 35mL/m^2) confirmed by other techniques eg. CMR, 3D TOE LVOT measurement, invasive data) - Calcium score by MSCT ≥ 3000 in men or ≥ 1600 in women: Severe AS Very likely ≥ 2000 in men or ≥ 1200 in women: Severe AS likely

Vmax:transvalvular peak velocity, MPG:mean transvalvular pressure gradient, AVA:aortic valve area, AVAi:aortic valve area indexed to body surface area, SVi:Stroke volume indexed to body surface area, CMR:Cardiac magnetic resonance imaging, TOE:Transoesophageal echocardiography, LVOT:Left ventricular outflow tract, MSCT:multi-slice computed tomography

Table 2: Baseline characteristics and primary endpoints of PRIMID-AS patients classified by combined ESC 2012/17 Criteria

	ESC 2012/17 Severity			
	Moderate n=50	Reclassified n=56	Severe n=68	P value
Patient Demographics				
Age	64.6±14.3	65.8±13.6	67.8±12.4	0.408
Female (%)	11 (22%)	12 (21.4%)	18 (26.5%)	0.768
Diabetes (%)	4 (8%)	9 (16.1%)	12 (17.6%)	0.305
Hypertension (%)	27 (54%)	32 (57.1%)	34 (50%)	0.727
Haemoglobin(g/dL)	14.4±1.3	14.4±1.2	14.1±1.3	0.291
eGFR (ml/min)	88.1±27	87.7±30.6	88.2±28.6	0.995
BMI (kg/m2)	28.4±3.5	27.7±4.1	27.9±4.6	0.695
SBP (mmHg)	145.5±19.5	146.4±22.6	148.3±21.1	0.756
DBP (mmHg)	77±10.6	77.4±11.3	77.1±10.3	0.979
Positive ETT (%)	14 (28.6%)	21 (37.5%)	21 (31.3%)	0.6
Echocardiography				
Stroke Volume Index (ml/m2)	53.5±9.3*	41±7.3†	51.2±13.1	<0.001
AVA (cm2)	1.4±0.2*†	1±0.2	1±0.3	<0.001
AVAI (cm2/m2)	0.7±0.1*†	0.5±0.1	0.5±0.1	<0.001
AV Vmax (m/s)	3.4±0.3†	3.6±0.2†	4.4±0.4	<0.001
MPG (mmHg)	26.3±5†	29.5±4.6†	46.9±12	<0.001
Mild AR	31 (62%)	39 (69.6%)	52 (76.5%)	0.2
Moderate AR	2 (4%)	0 (0%)	3 (4.4%)	
Mild MR	16 (32%)	19 (33.9%)	23 (33.8%)	0.97
Calcium Scores				
Calcium Score (AU)	1653 [783, 2573]†	1513 [1110, 2171]†	2962 [1785, 4349]	<0.001
Males Only	2064 [1385, 2708]†	1744 [1274, 2426]†	3303 [2366, 4806]	<0.001
Females Only	707 [348, 1091]†	934 [233, 1126]†	1829 [1301, 2562]	0.001
Biomarkers				
HsTnI (pg/ml)	3.95 [2.71, 8.71]†	5.19 [3.13, 9.27]†	7.10 [5.11, 11.13]	0.005
NTproBNP (pmol/L)	56.1 [16, 129]	46.3 [11.9, 143.5]	67.0 [21.3, 224.8]	0.407
CMR				
LVEF (%)	56.6±4.8	56.7±4.6	56.7±5.4	0.997
LVEDVI (ml/m2)	89±17.7	84.3±15.5	89.23±20.56	0.26
LVESVI (ml/m2)	38.9±10.6	36.7±9.1	39.06±11.78	0.424
LVM/LVEDV (g/ml)	0.62±0.1†	0.64±0.1†	0.71±0.1	<0.001
LVMI (g/m2)	55±12.3†	53.7±10.8†	63±15.5	<0.001
MPR	2.5±0.8†	2.4±0.6†	2±0.6	<0.001
ECV	24.9±2.4	25±2.5	24.7±2.5	0.837
iECV (ml/m2)	13.2±3.3	13.1±3.4	14.7±4.4	0.096
LGE (Y/N) (%)	21 (42%)	27 (48.2%)	34 (50%)	0.677
Primary Endpoint Y/N) (%)	6 (12%)	15 (26.8%)	26 (38.2%)	0.007

*significant difference to ‘Reclassified’ group; †significant difference to ‘Severe’ group. BMI:Body mass index, SBP:systolic blood pressure, DBP:diastolic blood pressure, ETT:exercise tolerance test, AVA:aortic valve area, AVAI:AVA index, AV Vmax:peak velocity, MPG:mean pressure gradient, AR:aortic regurgitation, MR:mitral regurgitation, HsTNI:high sensitivity troponin I, NTproBNP:N-terminal pro brain natriuretic peptide, LVEF:left ventricular ejection fraction, LVEDVI:LV end diastolic volume index, LVESVI:LV end systolic volume index, LVM/LVEDV:ratio of LV mass to end diastolic volume, LVMI:LV mass index, MPR:myocardial perfusion reserve, ECV:extra-cellular volume fraction, iECV:extra-cellular volume index, LGE:late gadolinium enhancement

Table 3: Adjusted univariate hazards of 'reclassified' or 'severe AS' groups to the primary endpoint compared to the 'moderate AS' group

	Model 1		Model 2	
	HR (95% CI)	p value	HR (95% CI)	p value
Reclassified*	2.78 (1.07-7.22)	0.036	2.60 (1.00-6.80)	0.051
Severe AS*	4.95 (2.02-12.13)	<0.001	5.11 (2.06-12.69)	<0.001
Female	2.10 (1.16-3.79)	0.014	2.02 (1.11-3.69)	0.022
Positive ETT	-	-	2.07 (1.14-3.75)	0.017

* compared to reference (moderate AS) group; all variables entered into model, Model 1: adjusted for sex, Model 2: adjusted for sex and positive ETT

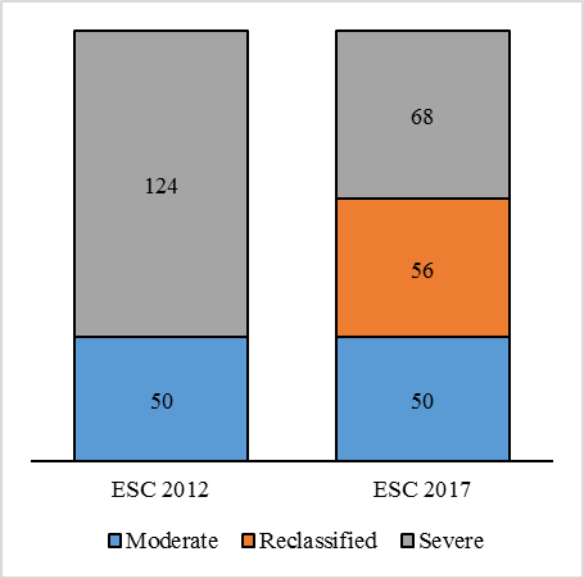
Table 4: Univariate Cox analyses in the Reclassified subgroup

	HR (95% CI)	p.value
Age (year)	1 (0.97-1.1)	0.37
Female (Y/N)	1.5 (0.45-4.7)	0.53
BSA (m2)	0.25 (0.02-3)	0.27
eGFR (ml/min/1.73m2)	0.99 (0.97-1)	0.29
Positive ETT (Y/N)	2.3 (0.82-6.5)	0.11
MPG (mmHg)	1.2 (1.1-1.4)	0.007
AV Vmax (m/s)	14 (0.92-200)	0.057
AVA (cm2)	0.06 (0.003-1.3)	0.071
AVAI (cm2/m2)	0.0091 (0.000014-6)	0.16
LVEF (per % increase)	1 (0.92-1.2)	0.58
Septal E/e' (per unit ratio change)	0.95 (0.83-1.1)	0.44
LVOT Area (cm2)	0.55 (0.23-1.3)	0.18
SVI (ml/m2)	1.1 (0.97-1.2)	0.18
LVMI (g/m2)	1 (0.97-1.1)	0.36
LVEDVI (ml/m2)	1 (0.97-1)	0.96
LVM/LVEDV (g/ml)	10 (0.05-2400)	0.4
Left atrial index (ml/m2)	1 (0.98-1)	0.34
LGE (Y/N)	1.2 (0.41-3.4)	0.76
MPR (per unit ratio change)	0.89 (0.34-2.3)	0.81
ECV (per unit ratio change)	1.2 (0.9-1.5)	0.26
High Calcium score (Y/N)	1.8 (0.65-5)	0.26
AVCalcIndex (per unit ratio change)	1.4 (0.88-2.1)	0.16
Log_2HsTnI	1.2 (0.81-1.7)	0.39
Log_2NTproBNP	1.1 (0.92-1.4)	0.23
MPG $\geq$ 31mmHg (Y/N)	7 (1.96-25)	0.003

Abbreviations as in Table-2.

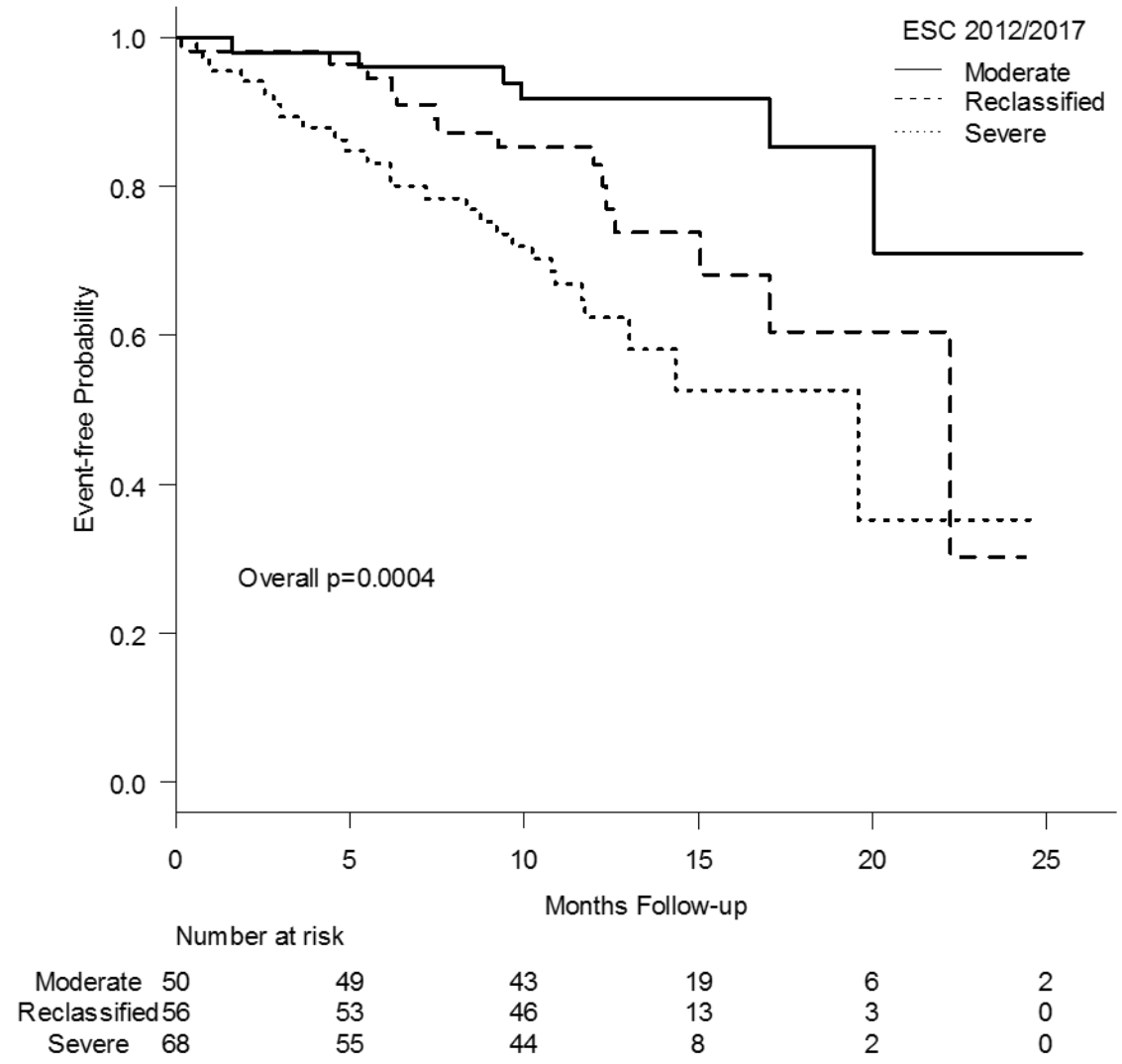
Figures

Figure 1: Severity distribution by different classification definitions



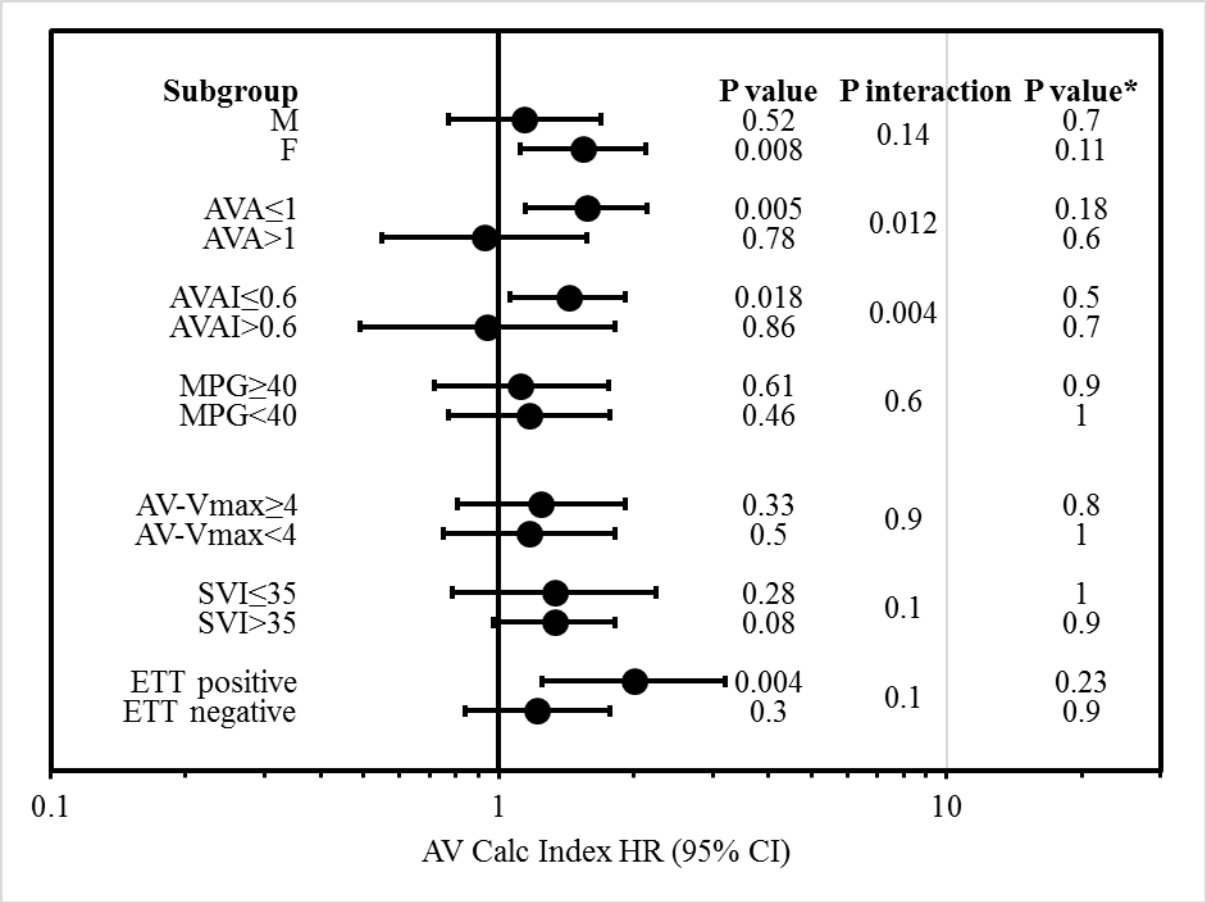
Reclassified: classified as severe AS in ESC 2012 but moderate AS in ESC 2017; ESC: European Society of Cardiology

Figure 2: Kaplan-Meier Curves for event-free probability by the three classes



Moderate vs Reclassified: p=0.053, Reclassified vs Severe: p=0.053, Moderate vs Severe: p=0.0007,

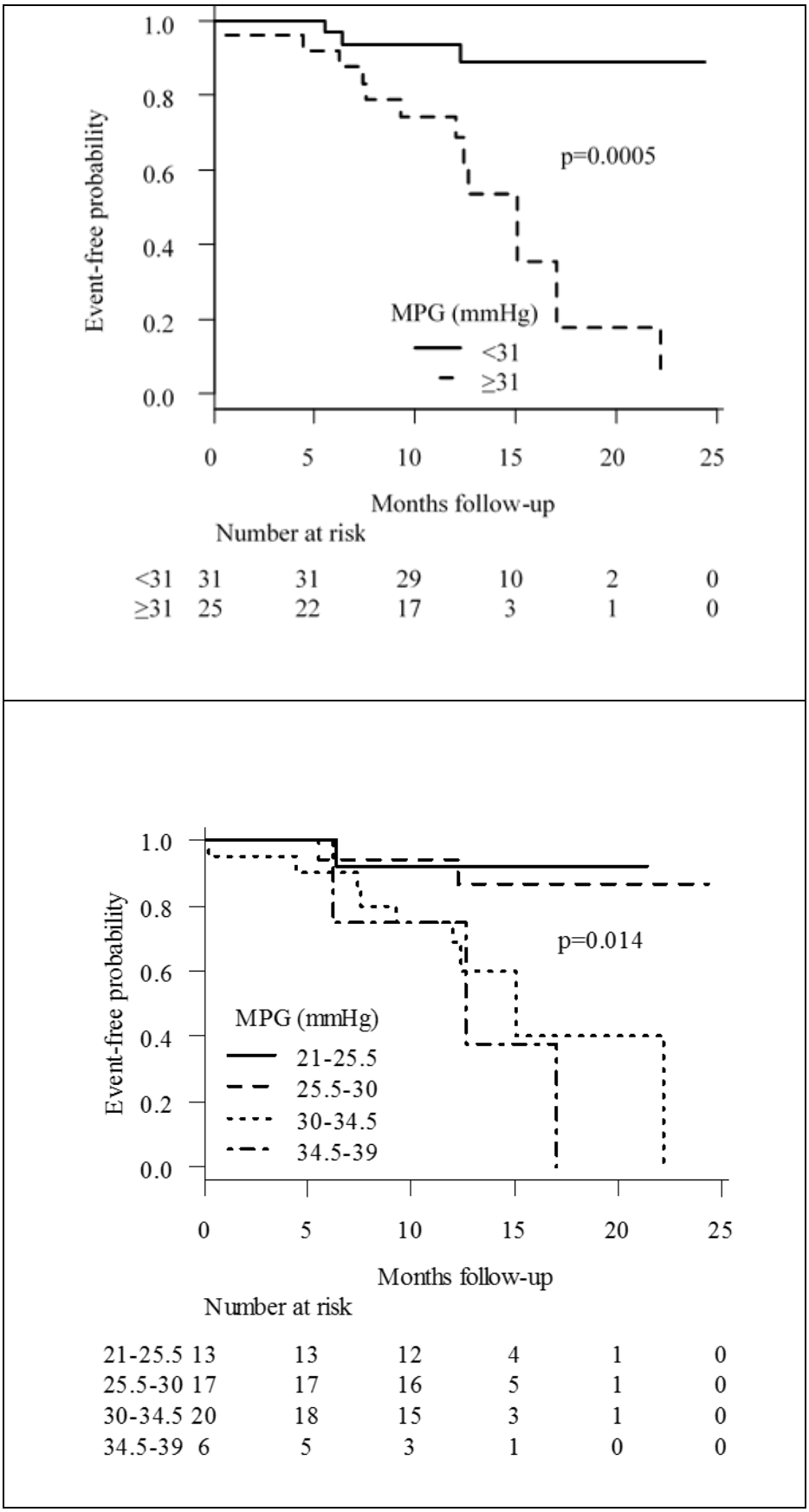
Figure 3: Subgroup analysis of additional prognostic value of AV Calc Index (unadjusted and adjusted)



Unadjusted hazard ratios of AVCalcIndex in specified subgroups. Abbreviations as in Table-2

*p-value after adjusting for AV-Vmax.

Figure 4: Kaplan Meier Analyses for Reclassified subgroup, grouped by MPG



MPG:mean pressure gradient