Predictors of Outcome in Patients with Moderate Mixed Aortic Valve Disease

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Word count: 3121

Running title: Predictors of outcome in moderate mixed aortic valve disease

Abstract

Objectives

Grading the severity of coexisting moderate aortic stenosis and regurgitation (MAVD) is challenging and the disease poorly understood. Identifying markers of haemodynamic severity will improve risk stratification and potentially guide timely treatment. This study aims to identify prognostic haemodynamic markers in patients with moderate MAVD.

Methods

Moderate MAVD was defined as coexisting moderate aortic stenosis (aortic valve area [AVA] 1.0-1.5cm^2) and moderate aortic regurgitation (vena contracta [VC] 0.3-0.6cm). Consecutive patients diagnosed between 2015-2019 were included from a multicentre registry. The primary composite outcome of death or heart failure hospitalisation was evaluated among these patients. Demographics, comorbidities, echocardiography and treatment data were assessed from their prognostic significance.

Results

207 patients with moderate MAVD were included, age 78 [66-84] years, 56% male sex , AVA 1.2 [1.1- 1.4]cm^2 and vena contracta 0.4 [0.4-0.5]cm. Over a follow up of 3.5 [2.5-4.7] years, the composite outcome was met in 89 patients (43%). Univariable associations with the primary outcome included older age, previous myocardial infarction, previous cerebrovascular event, atrial fibrillation, New York Heart Association >2, worse renal function and tricuspid regurgitation≥2 and mitral regurgitation ≥2. Markers of biventricular systolic function, cardiac remodelling, and trans-aortic valve haemodynamics demonstrated an inverse association with the primary composite outcome. In multivariable analysis, peak aortic jet velocity (V max) was independently and inversely associated with the composite outcome [hazards ratio (HR): 0.63,

95% confidence interval (CI): 0.43-0.93; p=0.021] in an adjusted model along with age [HR: 1.05, 95% CI: 1.03-1.08; p<0.001]:, creatinine [HR:1.002, 95% CI: 1.001-1.003; p=0.005], previous cerebrovascular accident [85 vs 42%; HR:3.04, 95% CI: 1.54-5.99; p=0.001] and left ventricular ejection fraction (LVEF) [HR: 0.97, 95% CI: 0.95-0.99; p=0.007]. Patients with V max ≤2.8m/s and LVEF ≤50% (n=27) had the worst outcome compared to the rest of the population [72 vs 41%; HR: 3.87, 95% CI: 2.20-6.80; P<0.001].

Conclusions

Patients with truly moderate MAVD have a high incidence of death and heart failure hospitalisation (43% at 3.5 [2.5-4.7] years). Within this group, a high risk group characterised by disproportionately low aortic V max (≤2.8m/s) and adverse remodelling (LVEF ≤50%) have the worst outcomes.

Key words: moderate mixed aortic valve disease, surgical aortic valve replacement, trans catheter aortic valve implantation, peak aortic valve velocity, risk stratification

Key Messages

What is already known on this topic

The severity of moderate MAVD is challenging to assess due to the haemodynamic and remodelling influences of each pathology. Consequently, risk stratification is incomplete.

What this study adds

We have identified a high risk group characterised by disproportionately low peak aortic valve velocity (≤2.8m/s) and adverse cardiac remodelling (left ventricular ejection fraction ≤50%) which are independently associated with mortality and heart failure hospitalisation. Patients with both adverse haemodynamic markers represent a high risk phenotype with an increased incidence of adverse outcomes.

How this study might affect research, practice or policy

Future studies need to validate our findings and evaluate whether including low peak aortic valve velocity (≤2.8m/s) and/or low left ventricular ejection fraction (≤50%) improve risk stratification in patients with moderate MAVD.

Abbreviations

AS- aortic stenosis

AR- aortic regurgitation

AVA- aortic valve area

AVR- aortic valve replacement

LVEF- left ventricular ejection fraction

MAVD- mixed aortic valve disease

MW FS- mid wall fractional shortening

TAVI- transcatheter aortic valve implantation

SAVR- surgical aortic valve replacement

VC- vena contracta

V max- peak aortic valve velocity

Introduction

Aortic stenosis (AS) and aortic regurgitation (AR) often coexist, termed mixed aortic valve disease (MAVD)[1]. Each individual pathology has a different natural history, left ventricular remodelling phenotype and criteria for intervention. AS results in pressure overload triggering a sequence of remodelling changes including left ventricular hypertrophy, focal and diffuse fibrosis and altered coronary haemodynamics [2]. AR causes mixed pressure and volume overload, resulting in left ventricular dilatation, eccentric hypertrophy and fibrosis [3]. Indications for aortic valve replacement in each disease are based on disease severity, symptom status and the impact on the left ventricle [4].

Moderate MAVD (moderate AS and AR) is common. However, there is a lack of guidance for grading disease severity and aortic valve replacement. Among patients with MAVD, indications for aortic valve replacement often rely on symptom status and the impact of the most dominant lesion [4,5]. Assessment of the severity of each lesion is complex due to the confounding haemodynamic effects of AR and AS. Volume overload associated with AR increases transvalvular flow, consequently increasing peak aortic velocity and overestimating the severity of AS. Left ventricular hypertrophy associated predominantly with AS, leads to impaired relaxation and therefore prolongs pressure half-time, underestimating the severity of AR. The impact on the myocardium is also complex due to the combination of pressure and volume overload on left ventricular remodelling. There is a paucity of data to risk stratify patients with moderate MAVD and subsequently guide management strategies [6]. Prior studies have included a heterogenous group of patients, ranging from mild to severe AR and moderate to severe AS [1,7–9]. Therefore, we sought to identify markers of outcome in patients with moderate MAVD.

Methods

We performed a retrospective, observational, multi-centre study using data from patients treated in North-East and Central London, United Kingdom (supplementary methods).

Consent

Ethical approval was obtained for this study and the need for informed consent waived due to the retrospective, observational nature of this study (North West – Greater Manchester South Research Ethics Committee; reference number: 21/NW/0182).

Study population

All adult patients aged 18 years or older who had moderate aortic stenosis and aortic regurgitation, identified using transthoracic echocardiography were included in this study. The inclusion criteria for this study used a multi-parametric echocardiographic approach to define moderate AS and AR based on international guidelines [4,10]. Patients who died within 1 month of their index scan were excluded (n=9) as we wanted to study the non-acute natural history of moderate MAVD. Patients that developed severe symptomatic disease or fulfilled any indication for valve replacement had either transcatheter aortic valve implantation (TAVI) or surgical aortic valve replacement (SAVR) as recommended by guidelines and a heart team discussion [4]. Patients not treated with aortic valve replacement were managed medically under routine surveillance.

Clinical investigations and treatment

All patients had comprehensive echocardiography in line with international guidelines [11–13]. Left ventricular volumes and ejection fraction (LVEF) were measured and calculated using Simpsons' Biplane method in the apical four and two chamber views. Left ventricular mass indexed was calculated using a previously described method [14] and shown in the

supplementary methods. The left ventricular outflow tract diameter was measured from the parasternal long axis view in early systole. The left ventricular outflow tract velocity time integral was measured using pulse wave Doppler in the apical 5 chamber view just below the aortic valve. V max was measured using continuous wave Doppler using multiple windows including apical, right parasternal and supra-sternal windows. Aortic valve area (AVA) was calculated using the continuity equation. Peak aortic gradients were calculated using the Bernoulli equation. Aortic valve regurgitation was quantified using an integrative approach incorporating qualitative and semi-quantitative data according to international recommendations [10]. Vena contracta was measured as the smallest diameter seen after the anatomical regurgitant orifice in either the parasternal long axis or apical 5 chamber view. Regurgitant volume and effective regurgitant orifice area were measured using the proximal isovelocity surface area method if feasible. Aortic valve flow rate was calculated using a method previously described elsewhere [15]. As an exploratory analysis we sought to evaluate stress-corrected mid wall fractional shortening (MW FS) to assess the impact of left ventricular contractility adjusted for haemodynamic stress. The formulas used to derive this have been proposed and described earlier [16,17]. We also sought to evaluate whether myocardial oxygen demand was an important factor in our population using a formula described elsewhere [18] (supplementary methods).

Data sources, definitions and study outcomes

Data on demographics, clinical comorbidities and treatment were identified from a local valve database. This is prospectively collected on all patients treated at our hospitals. Previous myocardial infarction was defined in line with the fourth universal definition for myocardial infarction [19]. Previous cerebrovascular event included both transient ischemic attacks and strokes. Pulmonary disease included any chronic lung condition that affected pulmonary

function or required ongoing therapy. Echocardiographic data was retrospectively obtained from clinically conducted scans. Data on all-cause mortality, cause of mortality and heart failure hospitalisation is nationally collected and was obtained from NHS Digital.

Low LVEF was defined as ≤50%, whilst normal LVEF was >50%. Low stroke volume indexed was defined as ≤35ml/m^2, whilst normal stroke volume was >35ml/m^2. Moderate MAVD was defined if a patient had both moderate AS (AVA 1.0-1.5cm^2) and moderate AR (vena contracta 0.3-0.6cm) based on universally recognised guidelines and using quantitative and semi-quantitative metrics [4].

The primary outcome of the study was a composite of all-cause mortality and hospitalisation for heart failure. The secondary outcome was a composite of cardiovascular mortality and hospitalisation for heart failure. Mortality due to a cardiovascular disease was based on the primary cause of death reported on the death certificate. Hospitalisation for heart failure was based on the primary reason for admission to hospital as reported using ICD-10 codes.

Patient and public involvement

Patients and the public were not involved in the design and conduct of this study.

Data availability statement

Data for this study is not available due to confidentiality reasons.

Statistical analysis

The study population was divided into those who met the primary outcome and those who did not. Baseline characteristics were compared between both groups. Normality of continuous variables was evaluated using the Shapiro-Wilk test and presented using mean ±

standard deviation for normally distributed variables and median [interquartile range] for non-normally distributed variables. Frequencies are presented as number (percentage). Normally distributed data were compared using the Student's t test, whilst non-normally distributed data were compared using the Mann-Whitney U test. In order to describe left ventricular remodelling in moderate MAVD, patients were divided into four groups according to relative wall thickness and left ventricular mass indexed. These included normal geometry, concentric remodelling, eccentric remodelling and eccentric hypertrophy as defined elsewhere (supplementary methods) [20].

The index time was the first echocardiogram that diagnosed moderate MAVD. For the primary study endpoint, univariable Cox regression analysis was performed on baseline characteristics that were significantly different between the two groups. Significant variables from this were included in multivariable Cox regression models, after excluding variables demonstrating multicollinearity. Multivariable models were created for clinical comorbidities and cardiac function and remodelling variables separately, before evaluating individual haemodynamic metrics along with all the significant variables. Multicollinearity and the proportional hazards assumption were checked using variance inflation factors and Schoenfeld residuals respectively. Two analyses were conducted; the first in the entire study population and the second among patients who had not been treated with aortic valve replacement, thus enabling an evaluation of the natural history of moderate MAVD. In order to determine the optimum cut-off value for significant haemodynamic metrics, receiver operating characteristic (ROC) curve analysis and Youden's index was applied. This value was used to stratify the study population and assess outcomes using Kaplan Meier analysis and the log Rank test. A 2-sided p value of <0.05 was deemed statistically significant. All analysis were performed using SPSS version 28.0 (SPSS, Chicago IL, United States).

Results

Baseline characteristics and remodelling

The study population consisted of 207 patients, age 78 [66-84] years, 56% male, (supplementary figure 1 shows how the population was derived). Patients had multiple comorbidities, LVEF 57 [55-61] %, aortic valve area (AVA) 1.2 [1.1-1.4] cm^2, vena contracta 0.4 [0.4-0.5] cm. Patients who met the primary outcome were older, had more comorbidities, more adverse cardiac remodelling and worse biventricular function (Table 1 and Figure 1). Normal geometry was the most frequent remodelling pattern (35%), followed by concentric remodelling (27%), concentric hypertrophy (26%) and eccentric hypertrophy (12%). Remodelling patterns were not different between the two groups (p=0.497).

Outcomes in the study population

Over a median follow up of 3.5 [2.5-4.7] years, 173 (84%) patients were managed under surveillance. 34 (16%) patients underwent aortic valve replacement (19 TAVI, 15 SAVR). During follow-up, 77 patients (37%) died, and 22 (11%) patients were hospitalised for heart failure. The primary outcome of all-cause death or heart failure hospitalisation occurred in 89 patients (43%).

Regarding mortality, 31 (40%) died due to cardiovascular causes and 46 (60%) due to non-cardiovascular causes. The secondary outcome of cardiovascular mortality or heart failure hospitalisation occurred in 50 patients (24%).

Associations with the primary outcome in the study population

Univariable regression analysis is shown in Figure 2. Significant variables were evaluated in multivariable models separately according to clinical factors and cardiac function and remodelling factors, demonstrating age, creatinine and previous cerebrovascular

events (85 vs 42%) and LVEF were independently associated with the primary outcome (supplementary table 1). Significant factors from these models were combined into a model where each haemodynamic metric of interest was tested separately (Supplementary table 2 and Figure 3).

Among echocardiographic factors, V max [hazards ratio (HR): 0.63, 95% confidence interval (CI): 0.43-0.93; p=0.021] and LVEF [HR: 0.97, 95% CI: 0.95-0.99; p=0.007] were independently associated with the primary outcome (Figure 3). Other haemodynamic metrics such as aortic valve mean gradient, stress corrected MW FS and flow rate were not significant in multivariable regression models. Whilst indexed stroke volume was significant as a continuous but not as a binary variable (indexed stroke volume $\leq$35ml/m^2).

Using ROC curve analysis and Youden's index, the optimal cut-off for V max was identified as 2.8m/s. A higher V max was associated with lower mortality or heart failure hospitalisation in an adjusted model [HR: 0.57, 95% CI: 0.35-0.91; p=0.008] (Figure 4). The study population was stratified into four groups according to V max and LVEF: V max $\leq$ and >2.8m/s and LVEF $\leq$ and >50%. Patients with low V max and impaired LVEF had the highest incidence of death or heart failure hospitalisation compared to the rest of the population (Log Rank p<0.001) (Figure 5). This group demonstrated a three-fold increase in adverse events compared to the group with high V max and normal LVEF, which had the best outcome [72 vs 41%; HR: 3.87, 95% CI: 2.2-6.8; p<0.001]. Although Kaplan Meier analysis showed that event curves diverged between the group with low V max and impaired LVEF and high V max and impaired LVEF, statistically there was no difference (Log rank p=0.217).

Association with the primary outcome among medically managed patients

Among 173 patients managed medically, significant prognostic markers were evaluated for their association with the primary outcome in order to validate their utility in this sub-population. Age, creatinine and previous cerebrovascular event (14 vs 2%) were significantly associated with the primary outcome. Additionally, LVEF [HR: 0.97, 95% CI: 0.95-1.00; p=0.02] and V max [HR: 0.61, 95% CI: 0.37-1.00; p=0.048] were inversely and independently associated with the primary outcome. A higher V max (>2.8m/s) was associated with lower mortality and heart failure [HR: 0.57, 95% CI: 0.35-0.91; p=0.018] whilst reduced left ventricular function (LVEF ≤50%) was associated with higher mortality and heart failure hospitalisation [HR: 2.28, 95% CI: 1.36-3.83; p=0.002] in an adjusted model (Supplementary figures 2-3).

Associations with the secondary outcome

A higher V max was associated with lower cardiovascular mortality or heart failure hospitalisation in an unadjusted analysis [HR: 0.46, 95% CI: 0.27-0.81; p=0.008]. After adjustment for LVEF ≤50% [HR: 2.43, 95% CI: 1.29-4.57; p=0.006], a higher V max showed a trend towards significance [HR: 0.56, 95% CI: 0.31-1.01; p=0.053]. Kaplan Meier analysis showed that the group with V max ≤2.8m/s and LVEF ≤50% continued to have the worst outcome (Log Rank p<0.001), (Figure 6).

Characteristics according to haemodynamic phenotype

Patients with the worst outcome (low V max and impaired LVEF) were compared to the rest of the study population to better characterise clinical characteristics and cardiac remodelling and function. Age and sex distribution were similar between both groups. The low V max and impaired LVEF group had a higher prevalence of previous myocardial infarction (41 vs 15%; p=0.003), lower relative wall thickness [0.37 (0.32-0.43) vs 0.44

(0.38-0.52), p=0.002] and lower stroke volume indexed (36 ± 12 vs 47 ± 12ml/m^2, p<0.001). Left ventricular diastology, other valvular dysfunction and right ventricular function was similar between both groups. The rate of aortic valve replacement was comparable between both groups (19 vs 16%, p=0.753) (Supplementary table 3).

Discussion

Patients with moderate MAVD have a high incidence of heart failure hospitalisation and death in the mid-term. Within this population, we have identified a high risk group characterised by both discordantly low peak aortic valve velocity (≤2.8m/s) and low left ventricular ejection fraction (≤50%) which are independently associated with mortality and heart failure hospitalisation, regardless of treatment. Patients with both adverse haemodynamic markers represent a high risk phenotype with worse outcomes.

Cardiac remodelling and function in moderate mixed aortic valve disease

Left ventricular remodelling in MAVD has not been well described. Our study has shown that the entire spectrum of left ventricular remodelling patterns can be present in moderate MAVD, indicating the heterogenous nature of this phenotype. The 'double hit' from increased preload and afterload in moderate MAVD adversely affects left ventricular geometry and function. Two-thirds of our patients had abnormal left ventricular remodelling, whilst one in five patients had impaired LVEF, demonstrating that moderate MAVD is not benign from a cardiac remodelling and functional perspective. It is important to note that myocardial contractility quantified using stress corrected mid wall fractional shortening (MW FS) was not independently associated with adverse outcomes. This is supported by similar myocardial oxygen consumption between patients with and without the primary outcome. The difference observed in our study between the clinical significance of LVEF and stress corrected MW FS

can be explained by LVEF representing as much a marker of remodelling as it is of systolic function. With its inherent flaws in the setting of cardiac hypertrophy and valvular heart disease [21], impaired LVEF in our population represents both a remodelled LV with reduced forward flow as demonstrated in supplementary table 3.

Risk stratification in moderate mixed aortic valve disease

Over a 3.5 year follow-up, nearly half of patients (43%) had a major clinical event and 1 in 4 patients had a major cardiac event, underscoring the significance of moderate MAVD. Most studies of MAVD have included a heterogenous group of patients ranging from mild AR to severe AR and moderate to severe AS (1,5,8,9,13,14). Many have reported composite endpoints of symptoms, aortic valve replacement (AVR) and death (5,9,10,13,14). Whilst each of these individual endpoints are important, AVR and symptoms are often strongly related and AVR can be disproportionately influenced by clinicians' interpretation of the investigational measures.

Several clinical prognostic markers were associated with mortality in our population-older age, poorer renal function and previous cerebrovascular accident. These non-cardiac prognostic factors are well recognised and contributed to the high incidence of non-cardiovascular death observed in our population. Peak aortic velocity reflects both the severity of AR by accounting for the increase in volume and AS by accounting for the degree of valvular obstruction. Previous studies have demonstrated its prognostic value in MAVD with higher velocities associated with an increased risk of mortality [8,22]. However, these studies included patients with moderate and severe aortic stenosis and/or regurgitation, where a higher V max indicates more severe AS whereas our study only included patients with moderate stenosis and regurgitation. We identified a group of patients with adverse features and very poor outcomes-those with both low aortic valve velocity (≤2.8m/s) and impaired LVEF (≤50%) had more left

ventricular remodelling, a higher prevalence of ischemic cardiomyopathy and lower transvalvular flow, suggesting a more adverse phenotype. These findings are similar to that observed in patients with classical low-flow, low-gradient aortic stenosis [25]. We therefore infer that patients with moderate MAVD, impaired LVEF and discordantly low V max are analogous to classical low-flow, low-gradient AS.

AVA has previously been suggested as a better marker for determining the severity of AS in patients with MAVD. The rationale being that metrics of transvalvular flow (stroke volume, flow rate, peak aortic velocity and mean gradient) are influenced by both AR and AS, whereas AVA can differentiate between increasing stroke volume, due to AR or increasing severity of AS [6,26]. However, AVA did not demonstrate an association with outcomes in our study.

Clinical implications of low peak aortic velocity and left ventricular systolic dysfunction

Timing of aortic valve replacement is key to reducing mortality, preventing heart failure and improving symptoms and quality of life. Moderate MAVD is not benign, especially amongst patients with low V max or impaired LVEF. Nonetheless, AVR for such lesions is not adequately covered in current guidelines because of a paucity of data. Incorporating LVEF and V max into risk stratification algorithms, may identify patients at highest risk of poor outcomes. Such patients may benefit from much closer follow up or even earlier AVR. However, our findings need to be validated by larger, prospectively designed studies and ideally evaluated in a clinical trial.

Limitations

This is a retrospective observational study and therefore is susceptible to uncontrolled bias and confounding. This study represents a single time assessment of baseline

characteristics, which over years are likely to change and therefore have a varying impact on outcomes and disease progression. Longitudinal studies that determine how patients progress in terms of symptoms, valve severity, cardiac remodelling and adverse cardiac events are required. Our study is not powered to make firm conclusions regarding multigroup comparisons and therefore our findings regarding low V max and low LVEF should be considered as hypothesis generating. The group with both low V max and low LVEF is small (n=27), again limiting the ability to draw firm conclusions for our findings. Given the observational nature of this study, our findings need to be validated by larger studies, especially the identification of a specific threshold of V max with prognostic implications that provides value to risk stratification and clinical decision making.

Conclusions

Patients with moderate MAVD have a poor outcome. A high risk group characterised by both disproportionately low aortic valve velocity (≤2.8ms) and adverse remodelling (LVEF ≤50%) represent a 'low-flow' phenotype with the worst outcomes. Larger studies are required to validate our findings.

Conflicts of interest

KPP has an unrestricted research grant from Edwards Lifesciences. TAT is directly and indirectly supported by the UCLH and Barts NIHR Biomedical Research Units. MJM has received grants and personal fees from Edwards Lifesciences and personal fees from Abbott Vascular.

Data availability statement

Data for this study is not available due to confidentiality reasons.

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Tables

Table 1: Baseline characteristics of study population

Parameters	All patients (n=207)	Alive and no HF hospitalisation (n=118)	Dead or HF hospitalisation (n=89)	P value
Demographics				
Age (years)	78 [66- 84]	**74 [59- 82]**	**84 [73- 88]**	**<0.001**
Male Sex	116 (56)	65 (55)	51 (57)	0.75
Comorbidities				
Creatinine (mmol/L)	93 [79- 121]	**91 [74- 116]**	**99 [82- 146]**	**0.039**
Dialysis	12 (5.8)	5 (4)	7 (8)	0.269
Pulmonary disease	50 (24.2)	23 (19)	27 (30)	0.071
Previous myocardial infarction	38 (18.4)	**16 (14)**	**22 (25)**	**0.04**
Previous cerebrovascular event	14 (6.8)	**2 (2)**	**12 (13)**	**0.001**
Diabetes	53 (25.6)	31 (26)	22 (25)	0.8
Hypertension	130 (62.8)	74 (63)	56 (63)	0.975
Atrial fibrillation	**50 (24.3)**	**18 (15)**	**32 (36)**	**<0.001**
NYHA 1	**100 (53.2)**	**69 (62.2)**	**31 (40.3)**	**0.018**
NYHA 2	**58 (30.9)**	**30 (27)**	**28 (36.4)**	
NYHA 3	**26 (13.8)**	**10 (9)**	**16 (20.8)**	
NYHA 4	**4 (2.1)**	**2 (1.8)**	**2 (2.6)**	
NYHA >2	**30 (16.0)**	**12 (10.8)**	**18 (23.4)**	**0.021**
Echocardiographic data				

Interventricular septum (cm)	1.1 [0.9- 1.3]	1.1 [0.9- 1.3]	1.1 [0.9- 1.3]	0.438
LV end diastolic diameter (cm)	4.7 [4.3- 5.1]	4.8 [4.3-5.2]	4.6 [4.2- 5.1]	0.118
LV end systolic diameter (cm)	3.2 [2.8- 3.6]	3.3 [2.7- 3.5]	3.2 [3.0- 3.7]	0.254
LV mass indexed (g/m^2)	97 [79- 116]	**92 [78- 114]**	**100 [83- 126]**	**0.049**
Relative wall thickness	0.43 [0.37- 0.51]	0.43 [0.36- 0.49]	0.43 [0.37- 0.55]	0.074
LV Ejection Fraction (%)	57 [55- 61]	**57 [55- 63]**	**55 [46- 58]**	**<0.001**
LVEF ≤50%	43 (20.8)	**17 (14)**	**26 (29)**	**0.009**
Stroke volume indexed (ml/m^2)	45 ± 12	**47 ± 12**	**42 ± 12**	**0.003**
Stroke volume indexed <35ml/m2	37 (17.9)	17 (14)	20 (22)	0.134
Flow rate (mls/s)	250 (216- 283)	**257 [225- 299]**	**237 [203- 269]**	**0.002**
E/A ratio	0.9 [0.7- 1.2]	0.85 [0.70- 1.20]	0.88 [0.72- 1.34]	0.356
E/e'	12 [9- 20]	**11 [8- 17]**	**15 [10- 23]**	**0.003**
Left atrial area (cm^2)	22 [19- 26]	**21 [18- 24]**	**24 [20- 27]**	**0.003**
Left atrial diameter (cm)	4.1 ± 1.0	**4.0 ± 1.0**	**4.3 ± 0.9**	**0.037**
MW FS (%)	17.1 (13.4- 21.5)	18.8 (14.3- 22.0)	16.0 (10.6- 20.0)	**0.003**
End systolic wall stress (kdynes/cm^2)	113 (87- 154)	116 (87- 161)	111 (84- 145)	0.376
Stress corrected MW FS (%)	**1.000 (0.786- 1.258)**	**1.097 (0.836- 1.289)**	**0.934 (0.620- 1.170)**	**0.003**
Myocardial oxygen consumption (g kdyne/cm^2 bpm)	1,356,228 (815,892- 1,966,222)	1,388,969 (900,811- 1,931,953)	1,318,399 (767,301- 2,051,011)	0.835
TAPSE (cm)	2.0 ± 0.5	**2.0 ± 0.5**	**1.9 ± 0.6**	**0.046**
PASP (mmHg)	31 [26- 41]	**29 [25- 36]**	**36 [28- 47]**	**<0.001**
Aortic peak velocity (m/s)	3.0 ± 0.6	**3.1 ± 0.5**	**2.8 ± 0.7**	**0.001**

Aortic peak gradient (mmHg)	37 [29- 47]	**39 [32- 48]**	**33 [25- 42]**	**0.001**
Aortic mean gradient (mmHg)	20 [15- 26]	**22 [17- 27]**	**18 [14- 24]**	**0.004**
Aortic valve area (cm^2)	1.2 [1.1- 1.4]	1.2 [1.1- 1.4]	1.2 [1.1- 1.3]	0.238
Vena contracta (cm)	0.4 [0.4- 0.5]	0.4 [0.4- 0.5]	0.4 [0.4- 0.5]	0.363
TR grade ≥2	60 (28.8)	**26 (22)**	**36 (38)**	**0.011**
MR grade ≥2	44 (21.2)	**19 (16)**	**25 (28)**	**0.037**
Treatment				
Aortic valve replacement	34 (16)	23 (19)	11 (12)	0.17

Data are presented as number (percentage), median [interquartile range] or mean ± standard deviation. LV- left ventricular, LVEF- left ventricular ejection fraction, TAPSE- tricuspid annular planar systolic excursion, MW FS- mid wall fractional shortening, PASP- pulmonary artery systolic pressure, TR- tricuspid regurgitation, MR- mitral regurgitation

Figure legends

Figure 1: box plots of key haemodynamics variables according to the primary composite outcome

Figure 2: Univariable associations for all-cause mortality and heart failure hospitalisation. All hazard ratios are per unit change in the continuous covariate or the presence of a binary covariate. LV- left ventricular, LVEF- left ventricular ejection fraction, SVi- indexed stroke volume, TAPSE- tricuspid annular planar systolic excursion, PASP- pulmonary artery systolic pressure, TR- tricuspid regurgitation, MR- mitral regurgitation

Figure 3: Multivariable regression model for the primary endpoint in the entire study population with continuous haemodynamic metrics

Figure 4: Multivariable regression model for the primary endpoint in the entire study population with binary haemodynamic metrics

Figure 5: Kaplan Meier analysis of echocardiographic phenotypes for all-cause mortality or heart failure hospitalisation. Low and high peak aortic velocity (V max) are defined as ≤ and > 2.8m/s respectively. Low and normal left ventricular ejection fraction (LVEF) are defined as ≤ and > 50% respectively.

Figure 6: Kaplan Meier analysis of echocardiographic phenotypes for cardiovascular death or heart failure hospitalisation. Figure 3: Low and high peak aortic velocity (V max) are defined as ≤ and > 2.8m/s respectively. Low and normal left ventricular ejection fraction (LVEF) are defined as ≤ and > 50% respectively.