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Comparison of exercise testing and CMR measured myocardial perfusion reserve for predicting outcome in asymptomatic aortic stenosis: the PRognostic Importance of MIcrovascular Dysfunction in Aortic Stenosis (PRIMID AS) study

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Abstract

Background: The management of asymptomatic patients with aortic stenosis (AS) remains controversial. Symptoms provoked on exercise testing is a class I indication for aortic valve replacement (AVR) but has low specificity. Cardiovascular Magnetic Resonance (CMR) measured Myocardial Perfusion Reserve (MPR) is an independent predictor of exercise capacity in patients with severe AS and inversely related to symptomatic class. **Aims:** To assess the prognostic value of MPR and exercise testing in asymptomatic patients with moderate-severe AS. **Method**: Multi-centre, prospective, observational study, with blinded analysis of CMR data. Patients underwent adenosine stress CMR, symptom-limited exercise testing (ETT) and echocardiography and were followed up for 12-30 months. The primary outcome was a composite of: typical AS symptoms necessitating referral for AVR, cardiovascular death and major adverse cardiovascular events. **Results**: 174 patients were recruited: mean age 66.2±13.34 years, 76% male, peak velocity 3.86±0.56 m/s and aortic valve area index 0.57±0.14 cm^2/m^2. A primary outcome occurred in 47 (27%) patients over a median follow-up of 374 (IQR 351-498) days. The mean MPR in those with and without a primary outcome was 2.06±0.65 and 2.34±0.70 (p=0.022), while the incidence of a symptom-limited ETT was 45.7% and 27.0% (p=0.020) respectively. MPR showed moderate association with outcome (area under curve (AUC)=0.61 (0.52-0.71, p=0.020), as did exercise testing (AUC=0.59 (0.51-0.68, p=0.027), with no significant difference between the two. **Conclusions**: MPR was associated with symptom-onset in initially asymptomatic patients with AS, but with moderate accuracy and was not superior to symptom-limited exercise testing. ClinicalTrials.gov (NCT01658345).

Key words: Aortic stenosis, exercise testing, magnetic resonance imaging, myocardial perfusion reserve

Introduction

The optimal management of asymptomatic patients with significant aortic stenosis (AS) remains controversial(1). Once symptoms develop there is a dramatic increase in the risk of sudden death which may occur before surgical intervention can be undertaken. A key goal of decision-making is to reliably identify those who are 'pre-symptomatic', so that intervention can be offered before the risk of sudden death and operative morbidity increase and the benefits from surgical intervention decrease. Exercise testing is the best-studied risk stratification tool in such patients. The recent American Heart Association (AHA)/American College of Cardiology (ACC) guidelines state that "*patients with symptoms provoked by exercise testing should be considered symptomatic*" and meet class-I recommendation for aortic valve replacement (AVR)(2), a view endorsed by the European Society of Cardiology (ESC) guidelines(3). Although patients with a truly negative exercise test have a low likelihood of developing symptoms in the short term, its positive predictive value for outcome is often poor (54-57%)(4-6).

Several recent studies have utilised the multi-parametric capability of cardiovascular magnetic resonance (CMR) imaging to better understand left ventricular (LV) remodeling and its consequences in AS. Late gadolinium enhancement (LGE) can detect replacement myocardial fibrosis that is associated with poor outcome following AVR(7, 8) and increased mortality independent of ejection fraction(9) or pre-operative symptom status(10). T1 mapping allows reproducible quantification of myocardial extracellular volume (ECV), a measure of diffuse fibrosis in AS(11, 12). We have also shown that myocardial perfusion reserve (MPR) measured by CMR was independently associated with exercise capacity and inversely with symptomatic class in patients with severe AS(13). These findings suggest that

CMR may be a clinically valuable imaging biomarker in stratifying asymptomatic patients with AS.

The aim of this study was to compare multi-parametric CMR with exercise testing to predict outcome in patients with asymptomatic AS. The primary hypothesis was that MPR would have a stronger association with symptom onset and major adverse cardiovascular events (MACE) than exercise testing.

Methods

The design and rationale of this study, the PRognostic Importance of MIcrovascular Dysfunction in asymptomatic patients with AS (PRIMID AS), has been reported previously(14). Briefly, PRIMID AS was a multi-centre, prospective, observational study conducted in 10 hospitals in the United Kingdom between April 2012 and November 2014.

Patients

Inclusion criteria were: ages 18 to 85 years, moderate to severe AS (≥2 of: aortic valve area <1.5 cm^2, peak pressure gradient >36 mmHg or mean pressure gradient >25 mmHg), asymptomatic and ability to perform bicycle exercise test. Exclusion criteria were: absolute contraindications to CMR, adenosine (severe asthma) or contrast administration (severe renal disease); previous cardiac surgery, LV ejection fraction <40%, persistent atrial flutter/fibrillation, other severe valve disease, previous heart failure, planned AVR or comorbidity limiting life expectancy or precluding AVR. The study was approved by the United Kingdom National Research Ethics Service (11/EM/0410) and all patients gave written informed consent prior to any testing. The study was registered on ClinicalTrials.gov (NCT01658345).

Investigations

Detailed phenotyping was performed at one of five regional centres offering a clinical CMR service (supplemental table-1). All investigations were done as research tests and reports were not routinely released to the responsible clinicians, so as not to influence patient management. An ECG and comprehensive trans-thoracic echocardiography (TTE), according to International guidelines, were performed.

Exercise testing

An incremental symptom-limited exercise tolerance test (ETT) was performed on a stationary bicycle as previously described(13). Patients were told: 'Breathlessness is labored or difficult breathing characterized by air hunger and an uncomfortable awareness of one's own breathing'. The ETT was considered symptomatically positive if the patient stopped prematurely due to limiting breathlessness or dizziness at <80% of their predicted workload or chest pain at any stage ('strict definition'). Given that the AHA/ACC/ESC(2, 3) guidelines consider symptoms at any stage indicative of symptoms, this 'conventional definition' of a symptomatically positive test was also considered. In patients who stopped because of fatigue, the ETT was classed as negative or inconclusive if ≥80% or < 80% of the predicted workload was achieved respectively.

CMR

A comprehensive stress CMR protocol was used (supplemental figure-1). CMR was performed on 3T platforms (supplemental table-1) as previously described(14). The protocol incorporated rest and adenosine stress perfusion, pre and post contrast T1 maps, LV function/mass and LGE.

Blood sampling

Patients had venepuncture for haematocrit, electrolytes and storage of plasma for NT-proBNP, analysed in a single batch at the end of the study, using our in-house non-competitive assay that employs the quantitative sandwich enzyme immunoassay technique, and has excellent correlation with the Roche Elecys assay.

Image Analysis

All images were analysed at the core lab in Leicester, blinded to patient details. Echocardiography was analysed by an accredited cardiac sonographer, using an Xcelera (Philips, Best, The Netherlands) workstation. Quantitative CMR analysis was performed by a single observer (AS). Volumetric, T1 mapping and LGE analysis was performed using *cvi42* version-5 (Circle Cardiovascular Imaging, Calgary, Canada) and perfusion analysis, to calculate rest and stress myocardial blood flow by model independent deconvolution, was performed using Q-mass version-7.1 (Medis, Leiden, Netherlands) as previously described(12, 13). The presence of LGE was agreed by two observers (AS, GPM) and quantified using the 5-standard deviation technique(15). Valvulo-arterial impedance (VAI) was calculated with stroke volume derived from both TTE and CMR(16).

Clinical follow-up

Patients were seen or contacted by telephone at 6 monthly intervals for a minimum of 12 months or until a pre-defined endpoint was reached, and a maximum of 30 months. A primary outcome was defined as a composite of typical AS symptoms necessitating referral for AVR, cardiovascular death or MACE (hospitalisation with heart failure, chest pain, syncope, arrhythmia). Referral for AVR in the absence of typical symptoms was considered a secondary endpoint. An independent events adjudication committee classified all events as a primary or secondary endpoint.

Statistical Analysis

Baseline data was collected using electronic case-record forms, and the blinded imaging data were sent to the Robertson Centre for Biostatistics, University of Glasgow, for unblinding and statistical analysis. Normally distributed data are expressed as mean±standard deviation. Non-parametric data are expressed as median (25%-75% interquartile range). Continuous variables were compared between patients with and without an outcome using independent t-tests or Mann-Whitney tests. The Chi-squared test or Fisher's exact test were used for categorical variables. Univariate and multivariable determinants of the primary outcome were determined using Cox proportional hazards regressions. The multivariable models were built using the stepwise selection approach based on adjusted chi-square statistics and consist of a series of alternating forward selection and backward elimination steps at p-to-enter and p-to-stay levels of 0.05. The following variables were included in the multivariable analyses: sex, NT-proBNP, one measure of AS severity, one CMR variable of LV remodeling, MPR and ETT. The stepwise models are included for descriptive purposes to illustrate the fact that only a small number of variables may be needed to explain the prognostic value of the baseline characteristics. We acknowledge that other models with different subsets of variables may have similar prognostic value. Kaplan-Meier curves were generated, using optimal cut-off for MPR, for event-free survival and compared using the log-rank test. The predictive accuracy of MPR and ETT for the primary outcome was assessed using logistic regressions and Receiver Operator Characteristic (ROC) analysis, with calculation of the area under the curves (AUC). The AUCs of MPR and ETT were compared using correlated ROC analysis. Additional sensitivity analyses were performed in patients with severe AS only. The study, with 170 subjects would have 80% power (binomial test) to show that MPR had superior overall accuracy (assumed 85%) to ETT, compared to the results of previous studies (76%) assuming an annual event rate of 29%(5).

Results

Clinical outcomes

A total of 174 patients were recruited (figure-1, table-1) of whom 123 (71%) met at least one criterion for severe AS(3). During a median follow-up of 374 (IQR 351-498) days the primary outcome occurred in 47 (27.0%) patients: all but one developed symptoms and 2 died. A secondary outcome occurred in 60 (34.5%) patients with 13 having AVR whilst asymptomatic. Despite constituting only 23.6% of the participants, females accounted for 38.3% of those who developed a primary outcome. These patients also had more severe disease, with higher gradients and lower valve area, higher NT-proBNP, lower haemoglobin and eGFR.

ETT

There were no medical complications during exercise testing, which was performed by all but two patients. The reasons for stopping were: fatigue/discomfort (114), dyspnoea (n=51), chest pain (n=4), bigeminy (n=2) and hypertension (n=1). Thirty per cent of the patients had an inconclusive exercise test. Patients with a primary outcome had a greater proportion of symptomatically positive tests (using both definition) (table-2).

CMR

CMR was completed in all participants without complications. MPR was not analysable in nine patients. Patients with a primary outcome displayed lower stroke volumes, with similar indexed LV volumes and mass (table-2). Global MPR was significantly lower in the outcome group (2.06 ± 0.65 *vs.* 2.34 ± 0.70, p = 0.022). There was no significant difference in the frequency and quantity of scarring assessed with LGE. Fifty-three patients did not have T1 mapping performed due to unavailability of the pulse sequence at one site for part of the study. ECV was not significantly higher in those with an outcome.

Comparison of MPR and ETT

ROC curves for MPR and ETT for the primary outcome are shown in figure-2. The negative and inconclusive ETTs were grouped together and compared to positive ETTs. The AUC for MPR was statistically significant: 0.61, (0.52-0.71), p=0.020 with an optimal cut-off of 2.10. The AUC for ETT were: 0.59 (0.51-0.68), p=0.027 ('conventional' definition) and 0.56 (0.50-0.62), p=0.070 ('strict' definition). Event-free survival was significantly lower in those with low MPR and a positive ETT (figure-3). The specificity, sensitivity, positive predictive value (PPV) and negative predictive value (NPV) are shown in table-3. Both MPR and positive ETT had high NPV, but low PPV. The strict definition had a very high specificity but very low sensitivity. Similar results were seen for the 123 patients with severe AS. (supplemental table-3). There was no significant difference between the AUCs of MPR and ETT using correlated ROC analysis (0.05(-0.06-0.17, p=0.345) for strict definition and 0.03(-0.11-0.17, p=0.677) for conventional definition).

Univariate associations with primary outcome

Both symptom-limited ETT and low MPR were univariate predictors of the primary outcome after adjusting for sex (table-4). Increasing AS severity, increased mass/volume ratio, VAI, NT-proBNP and resting LV rate pressure product were also associated with the primary outcome.

Multivariable associations with primary and secondary outcomes

The following variables were included in the stepwise analysis model: sex, NT-proBNP, aortic valve area index (AVAI), MPR, LV mass/volume ratio and positive ETT. Gender and AVAI remained independent predictors of outcome, with positive ETT also being a predictor using the strict definition only, and NT-proBNP using conventional definition (table-4). The results did not change when AS severity was entered into the model instead of AVAI, other

than NT-proBNP was also independently associated with outcome using the strict definition on ETT.

In patients with severe AS only, AVAI remained an independent predictor, with the addition of gender and positive ETT for strict definition only (supplemental table-4). For the secondary outcome, AVAI, MPR and symptomatically positive ETT (strict and conventional definitions) were independent predictors of the combined endpoint of all AVR/symptoms and MACE (supplemental table-2).

Discussion

A number of studies have linked LV remodeling, and particularly myocardial fibrosis, with adverse outcome in AS. This is the first prospective study to explore the hypothesis that CMR could predict the development of symptoms in asymptomatic patients with AS. MPR is an independent predictor of exercise capacity and inversely associated with NYHA class in patients with severe AS undergoing AVR(13). In this study we have confirmed that low MPR in initially asymptomatic patients is also associated with the development of symptoms in the medium term. However, the accuracy of MPR to predict outcome was moderate at best and, contrary to our primary hypothesis, not significantly better than exercise testing. This is also the largest cohort of patients with asymptomatic moderate-severe AS to date to have undergone both exercise testing and CMR. The primary endpoint occurred in 27% of patients and the secondary endpoint in 35%, and is comparable to that seen in previous reports(5, 6).

Exercise testing

It may be surprising that exercise testing to identify 'pre-symptomatic patients' performed poorly in this study, given the class-I indication for surgery in the major International guidelines. It is worth noting that the 2014 AHA/ACC guidelines re-classified symptoms on

exercise testing from a class IIb to a class I indication for AVR, which was after the commencement of our study and when ETT was not widely adopted in our institutions. However, our results are largely consistent with the published literature. A normal exercise test has a high negative predictive accuracy (ranging from 0.86-1.00 in previous studies compared to 0.79 in ours)(4, 6, 17), suggesting that these patients can be safely managed conservatively. However, although patients who develop symptoms on exercise testing are at higher risk of developing spontaneous symptoms or experiencing MACE, the specificity of a positive test is low (0.60-0.78 in previous studies compared to 0.73 in ours)(4, 5). In this study, only 20 of 55 patients who had a positive test using a conventional definition developed spontaneous symptoms during follow-up. The results were consistent in a sensitivity analysis of patients with severe AS as well (specificity 0.71). If current guidelines were followed, many patients may be sent for early surgery unnecessarily, as the majority of patients with a positive test did not develop spontaneous symptoms in the medium term. This calls into question the recommendation of exercise-induced symptoms as a class-I indication for AVR(2, 3), which is not based on data from randomised controlled trials. Previous studies looking at the prognostic value of exercise testing in AS have generally been single-centre studies, with relatively small numbers of patients (n=30-160)(4, 6, 16, 17). Another disadvantage of ETT is the high proportion of patients with inconclusive results (30%), despite restricting inclusion to those who can exercise, which reflects the subjective nature and limitation of the test in the real world.

As previously demonstrated(6), echocardiographic measures of severity are important predictors of outcome but with wide overlap in those who do and do not develop symptoms. Only one other study has identified female gender as increasing risk of symptoms(18). Female patients may have a different remodeling process, as suggested by lower cardiac

volumes and more concentric LV geometry than men(19). This may suggest a need for gender-specific cut-offs for definition of severity. Female patients also tend to perform less well on exercise testing(20), and may therefore be more likely to be labelled as having an inconclusive test, and not identified as high risk until a later stage.

CMR predictors of outcome

This is the first CMR study assessing the prognostic value of MPR, LGE and ECV in asymptomatic patients with AS. MPR was significantly lower in the primary outcome group, a univariate predictor of outcome, as well as there being significant survival difference in those with a low and high MPR on Kaplen-Meier analysis. ROC analysis also demonstrated statistically significant AUC for MPR to predict the primary outcome. Two previous studies have shown TTE measured coronary flow reserve (CFR) to be independently associated with mortality in patients with moderate to severe AS, though the numbers were small with significant other limitations(20, 21).

LGE and ECV in this study were not associated with the primary outcome. Although LGE has been shown to predict poor outcome, this has been almost exclusively in patients with severe AS who have undergone AVR(7, 8). In that context LGE represents replacement fibrosis and is likely indicative of irreversible LV dysfunction. There has been intense interest in quantification of ECV, a surrogate of diffuse interstitial fibrosis, and its relationship to clinical outcomes in a range of cardiac conditions, especially AS(11). We saw only a very small difference in ECV (1%) between those with and without an outcome and have previously shown that ECV is not increased in asymptomatic patients with AS, compared to age and sex-matched controls(12). The normal range of ECV is in the order of 25%, and there is very wide overlap between patients and healthy controls and therefore it is likely to be insensitive to small increases in interstitial fibrosis. So, although ECV may detect differences in populations, it is unlikely to be of clinical value in individual patients unless

they have extreme values, such as in amyloidosis(22). The lack of association of LV mass and volumes with outcome is again likely to be related to the high event rate in female patients, who have smaller hearts even when indexed to body size.

Strengths

This was a prospective, multicentre study, and although observational, was run from outset to the same standards as a randomised controlled trial. The CMR and ETT results were blinded to the clinicians, imaging tests were analysed in a core lab, and there was independent event adjudication and statistical analysis. We also recruited a well-described population who were regarded as low risk (in whom prophylactic AVR may be offered) and were prepared to have surgery should symptoms develop. Finally, the primary endpoint was carefully defined and excluded those being referred for AVR prior to the onset of spontaneous symptoms, which is a soft endpoint.

Limitations

Although this study was large for its kind, the number of clinical events was relatively small and this limits the number of variables that could be entered into the multivariable model. The inclusion of patients with moderate disease may be criticised, however, these patients do have high event rates and the results of the study were consistent when only the 123 patients with severe AS were analysed. There was also missing data (T1 mapping) due to technical problems during the study, but his did not affect the primary outcome analysis. Finally, although there was a statistically significant difference in MPR between those with and without an outcome, the difference was small with large overlap between the two groups, somewhat limiting its clinical use.

Conclusions

CMR measured MPR and symptom-limited exercise testing are associated with clinical outcome in initially asymptomatic patients with moderate-severe AS. However, predictive accuracy is moderate at best and MPR is not superior to symptom-limited exercise testing. Further refinement of risk-stratification is required in asymptomatic AS.

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Disclosures

All authors have completed ICMJE form for disclosure with regards to this manuscript. There are no disclosures of conflict of interest to declare in relation to this manuscript.

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Legends

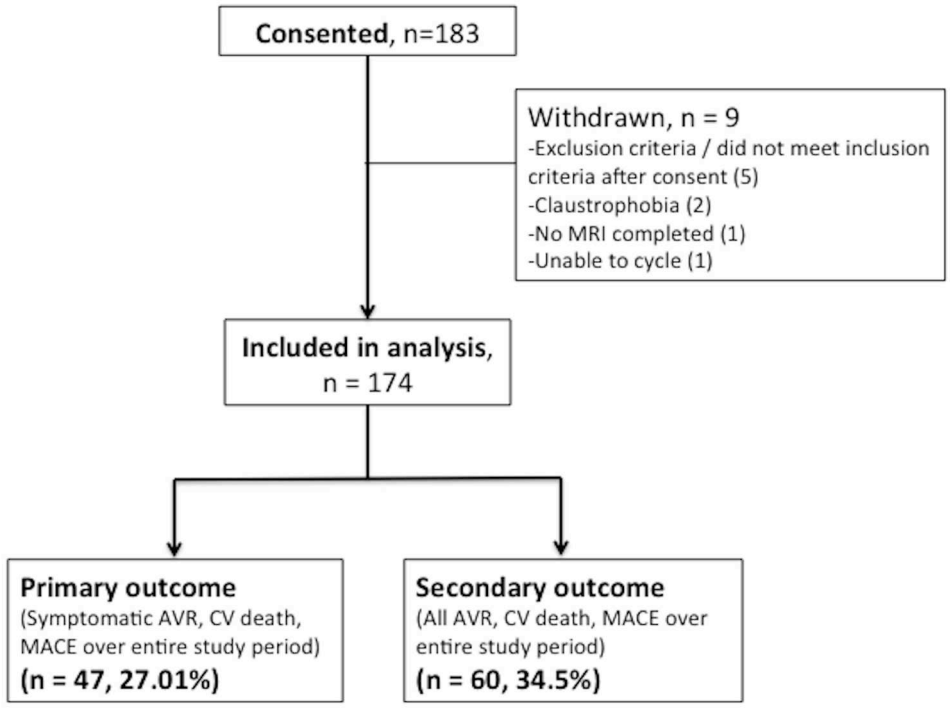

Figure 1. Recruitment flowchart

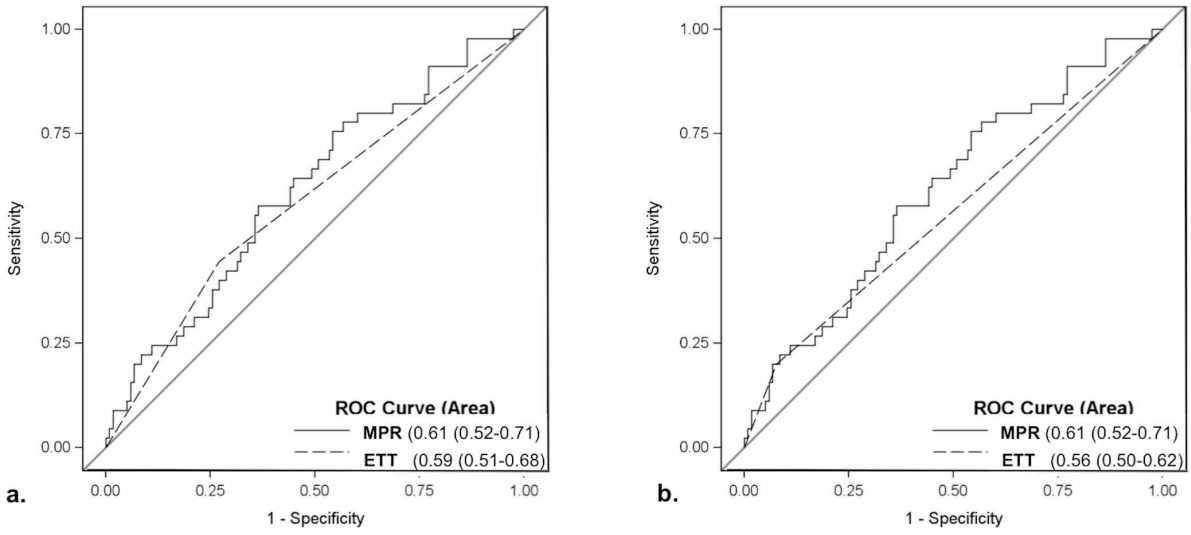

Figure 2. ROC curves for MPR and symptom-limited ETT (a. conventional definition, b. strict definition) for predicting the primary outcome

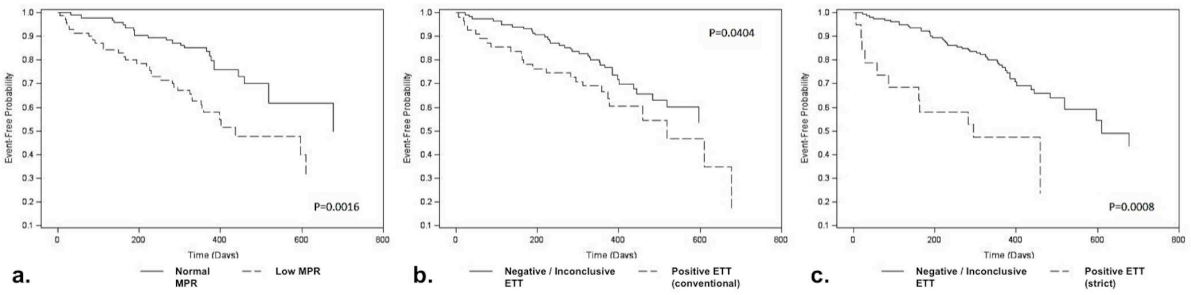

Figure 3. Kaplan-Meier curves for event-free survival for those a.) above and below MPR cut-point of 2.098, b.) symptom-limited ETT (conventional definition) and c.) symptom-limited ETT (strict definition)

Table 1. Demographic and echocardiography data

	All patients (n=174)	**Primary outcome** (n=47)	**No primary outcome** (n=127)	**p-value**
Demographic data				
Age (years)	66.2 ± 13.34	68.7 ± 11.54	65.3 ± 13.89	0.144
Male (n (%))	133 (76.4)	29 (61.7)	104 (81.9)	0.005*
BSA (m^2)	2.0 ± 0.21	1.9 ± 0.18	2.0 ± 0.21	0.034*
Resting HR (bpm)	70.3 ± 11.43	70.1 ± 13.80	70.4 ± 10.47	0.918
Resting SBP (mmHg)	146.9 ± 21.09	147.3 ± 22.80	146.8 ± 20.51	0.886
Resting DBP (mmHg)	77.2 ± 10.65	75.2 ± 10.80	77.9 ± 10.54	0.148
Diabetes (n (%))	25 (14.4)	8 (17.0)	17 (13.4)	0.544
Hypertension (n (%))	93 (53.4)	25 (53.2)	68 (53.5)	0.967
Hyperlipidaemia (n (%))	92 (52.9)	22 (46.8)	70 (55.1)	0.577
ACE-I/ARB (n (%))	77 (44.3)	18 (38.3)	59 (46.5)	0.336
Beta-blocker (n (%))	54 (31.0)	19 (40.4)	35 (27.6)	0.103
Statin	105 (60.3)	27 (57.4)	78 (61.4)	0.635
NT-proBNP (pmol/L)	56.51 (19.22, 152.52)	129.97 (36.86, 254.31)	48.69 (17.18, 124.47)	0.008*
Hb (g/dL)	14.2 ± 1.24	13.9 ± 1.14	14.4 ± 1.25	0.016*
eGFR (ml/min)	88 ± 28.6	79 ± 19.2	91 ± 30.8	0.004*
Echocardiography data				
AV Vmax (m/s)	3.86 ± 0.56	4.13 ± 0.61	3.76 ± 0.51	<0.001*
MPG (mmHg)	35.4 ± 12.49	41.5 ± 14.15	33.1 ± 11.04	<0.001*
AVAI (cm^2/m^2)	0.57 ± 0.14	0.51 ± 0.15	0.59 ± 0.13	0.001*
E/A	0.88 ± 0.29	0.85 ± 0.30	0.89 ± 0.28	0.388
Septal E/e'	12.28 ± 4.86	13.23 ± 5.61	11.92 ± 4.52	0.125
Lateral E/e'	9.88 ± 3.72	10.59 ± 3.44	9.62 ± 3.80	0.137
VAI (Echo) ($mmHg/ml/m^2$)	3.96 ± 1.06	4.18 ± 1.18	3.88 ± 1.00	0.096

Abbreviations: BSA=body surface area, HR=heart rate, SBP/DBP=systolic/diastolic blood pressure, ACE-I=angiotensin converting enzyme inhibitor, ARB=angiotensin II receptor blocker, NT-proBNP=N terminal brain natriuretic peptide, Hb=haemoglobin, eGFR=estimated glomerular filtration rate, AV Vmax=peak aortic jet velocity, MPG=mean pressure gradient, AVAI=aortic valve area indexed to BSA, VAI=valvulo-arterial impedance. (* $p<0.05$ between outcome and no outcome groups)

Table 2. Exercise test and cardiovascular magnetic resonance imaging data

	Primary outcome (n=47)	No primary outcome (n=127)	p-value
ETT data			
Exercise duration (min)	8.45 ± 2.55	8.51 ± 1.79	0.892
Peak workload (W)	96 ± 33.7	115 ± 41.2	0.006*
% predicted workload (%)	85.4 ± 25.6	86.7 ± 28.2	0.775
% predicted HR (%)	87.4 ± 11.9	86.5 ± 11.8	0.657
Rise in SBP (mmHg)	37 ± 24.8	43 ± 21.0	0.098
Positive ETT (strict) (%)	19.6	7.9	0.031*
Positive ETT (conventional) (%)	45.7	27.0	0.020*
CMR data			
LVEDVI (ml/m²)	84.47 ± 15.38	88.73 ± 19.16	0.173
LVESVI (ml/m²)	36.15 ± 9.20	39.07 ± 11.07	0.109
LVSV (ml)	92 ± 16.2	99 ± 25.1	0.033*
LVSVI (ml/m²)	48.29 ± 7.79	49.68 ± 9.82	0.383
LVEF (%)	57.5 ± 4.60	56.4 ± 5.05	0.167
LVMI (g/m²)	57.14 ± 12.15	57.90 ± 14.46	0.750
LV mass/volume (g/ml)	0.68 ± 0.13	0.66 ± 0.10	0.146
LAVI (ml/m²)	57.31 ± 17.33	54.05 ± 13.61	0.251
VAI (MRI) (mmHg/ml/m²)	4.00 ± 0.80	3.74 ± 0.82	0.065
Global MPR	2.06 ± 0.65	2.34 ± 0.70	0.022*
Global stress MBF (ml/min/g)	2.05 ± 0.64	2.20 ± 0.72	0.216
Global rest MBF (ml/min/g)	1.05 ± 0.36	0.96 ± 0.22	0.119
LGE present (n,%)	24 (51.1)	58 (45.7)	0.527
% LGE (%)	4.4 ± 3.19	4.2 ± 3.96	0.683
Native T1 (ms)	1114.3 ± 61.13	1139.4 ± 71.85	0.070
ECV (%)	25.35 ± 2.53	24.60 ± 2.37	0.132

Abbreviations: ETT=exercise tolerance test, LVEDVI=left ventricular end-diastolic volume indexed to BSA, LVESVI=left ventricular end systolic volume indexed to BSA, LVSI=left ventricular stroke volume indexed to BSA, LVEF=left ventricular ejection fraction, LVMI=left ventricular mass indexed to BSA, LAVI=left atrial volume indexed to BSA, VAI=valvulo-arterial impedance, MPR=myocardial perfusion reserve, MBF=myocardial blood flow, LGE=late gadolinium enhancement, ECV=extracellular volume fraction. (* $p<0.05$)

Table 3. Sensitivity, specificity, positive and negative predictive value of MPR and exercise testing for predicting the primary outcome

Parameter	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
MPR	0.59 (0.43, 0.73)	0.63 (0.54, 0.72)	0.38 (0.27, 0.50)	0.80 (0.70, 0.87)
Positive ETT (strict)	0.20 (0.09, 0.34)	0.92 (0.86, 0.96)	0.47 (0.25, 0.71)	0.76 (0.68, 0.82)
Positive ETT (conventional)	0.46 (0.31, 0.60)	0.73 (0.64, 0.81)	0.38 (0.25, 0.52)	0.79 (0.70, 0.86)

Abbreviations: PPV=positive predictive value, NPV=negative predictive value, MPR=myocardial perfusion reserve, ETT=exercise tolerance test. Sample size for MPR=165, for ETT=172.

Table 4. Univariate (adjusted for sex) and multivariable associations of primary outcome (model 1: strict definition ETT, model 2: conventional definition ETT)

Variable	Univariate		Multivariable-model 1		Multivariable-model 2	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Gender (M *vs.* F)	0.47 (0.26 - 0.84)	0.011	0.42 (0.22 - 0.79)	0.008	0.54 (0.29 - 0.99)	0.045
AV Vmax	3.25 (1.99 - 5.31)	<0.001				
MPG	1.05 (1.03 - 1.07)	<0.001				
AVAI	0.63 (0.50 - 0.80)	<0.001	0.61 (0.47 - 0.80)	<0.001	0.60 (0.47 - 0.77)	<0.001
VAI (Echo)	1.30 (1.04 - 1.63)	0.024				
VAI (CMR)	1.42 (1.02 - 1.98)	0.035				
LV mass / Volume	1.32 (1.04 - 1.68)	0.023				
MPR	0.62 (0.39 - 0.97)	0.035				
Log (NT-proBNP)	1.28 (1.05 - 1.56)	0.015			1.22 (1.00 - 1.48)	0.048
Positive ETT (strict)	4.17 (1.92 - 9.05)	<0.001	3.41 (1.55 - 7.50)	0.002		
Positive ETT (conventional)	1.90 (1.06 - 3.42)	0.032				
Resting LVRPP	2.89 (1.14 - 7.37)	0.026				

Abbreviations: As tables 1 and 2