National Institute for Health and Care Excellence

Draft

Heart valve disease presenting in adults: investigation and management

[E] Evidence review for stress testing and stress echocardiography in determining need for intervention

NICE guideline <number>

Prognostic evidence review underpinning recommendations 1.3.2, 1.3.3 and 1.3.8 and research recommendations in the NICE guideline

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Draft for Consultation

These evidence reviews were developed by the National Guideline Centre, hosted by the Royal College of Physicians

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1 Stress testing and stress echocardiography in determining the need for intervention

1.1 Review question

In adults with heart valve disease, what is the prognostic value and cost effectiveness of stress testing and stress echocardiography to determine the need for intervention?

1.1.1 Introduction

In the absence of symptoms, severe heart valve disease may not need an intervention. However, symptoms begin to occur on exertion, so sedentary patients may only experience symptoms late in the course of the disease. Stress testing may reveal reduced exercise tolerance and symptoms and stress echocardiography may reveal a higher haemodynamic impact of the severe heart valve disease compared with echocardiography at rest. Furthermore, in symptomatic patients with non-severe heart valve disease diagnosed on echocardiography at rest, stress echocardiography may reveal a dynamic component or reclassify the heart valve disease as severe. Consequently, it is important to define the prognostic value and cost effectiveness of stress testing and stress echocardiography to determine the need for intervention, when the symptomatic status and the severity of the heart valve disease on echocardiography at rest are discordant.

1.1.2 Summary of the protocol

For full details see the review protocol in Appendix A.

Table 1: PICO characteristics of review question

Population	Adults 18 years or over with diagnosed heart valve disease requiring further tests after echocardiography to determine if intervention is required, either because they are symptomatic but do not have severe HVD or are asymptomatic with severe HVD. Stratified as follows: • Asymptomatic severe aortic (including bicuspid) stenosis • Symptomatic non-severe aortic (including bicuspid) stenosis • Asymptomatic severe aortic regurgitation • Asymptomatic severe mitral stenosis • Symptomatic non-severe mitral stenosis • Asymptomatic severe mitral regurgitation • Symptomatic non-severe mitral regurgitation <u>Inclusion of indirect evidence:</u> Studies including mixed populations will be included (and downgraded for indirectness) if >75% of the included patients meet the protocol criteria. If limited evidence is available, studies with a mixed severe/non-severe population (including mixed moderate/severe) or mixed symptomatic status will be considered for inclusion with downgrading for indirectness <u>Exclusion:</u> Children (aged less than 18 years). Adults with congenital heart disease (excluding bicuspid aortic valves).

	Tricuspid stenosis and pulmonary valve disease. Adults with previous intervention for HVD (surgical or transcatheter) For asymptomatic heart valve disease, secondary heart valve disease because it does not occur in the asymptomatic group Adults with acute heart failure
Prognostic variables under consideration	The following parameters will be assessed according to the type of HVD. Functional and anatomical parameters refer to measurements from pharmacological stress or exercise echocardiography: <u>1. Mitral regurgitation</u> **Asymptomatic severe MR** Exercise stress testing: • Exercise capacity <60% predicted workload for gender, age and weight • Symptoms unmasked in response to exercise • Increase in BNP levels on exercise compared with baseline • Development of significant arrhythmia on exercise Exercise stress echocardiography: • Decrease in LVEF on exercise compared with baseline • Reduced left ventricular systolic function based on global longitudinal strain on exercise compared with baseline • Increase in peak systolic pulmonary artery pressure during low workload exercise to >60 mmHg (SPAP >60 mmHg) • Lack of demonstrated contractile reserve at low workload exercise **Symptomatic non-severe MR** Exercise or pharmacological stress testing: • Exercise capacity <60% predicted workload for gender, age and weight • Increase in BNP levels on exercise compared with baseline Exercise stress echocardiography: • Severe status unmasked in response to pharmacological stress or exercise <u>2. Aortic stenosis</u> **Asymptomatic severe AS** Exercise stress testing: • Exercise capacity <60% predicted workload for gender, age and weight • Symptoms unmasked in response to exercise • Increase in BNP levels on exercise compared with baseline • Reduction of blood pressure by >20 mmHg or no rise in blood pressure during exercise • ST depression on ECG by >2 mm during exercise in the absence of coronary disease • Development of significant arrhythmia on exercise Exercise stress echocardiography:

- Decrease in LVEF on pharmacological stress or exercise compared with baseline
- Reduced left ventricular systolic function based on global longitudinal strain on pharmacological stress or exercise compared with baseline
- Worsening in parameters of diastolic function / indicators of left atrial filling pressure (E/e') on exercise compared with baseline – E/e' >15 on exercise
- Mean gradient increase >20mmHg during exercise
- Induced ischaemia (regional wall motion abnormalities) during exercise in the absence of coronary disease
- Development of moderate or severe mitral regurgitation on exercise

Symptomatic non-severe or low-flow AS

Exercise stress testing:

- Exercise capacity <60% predicted workload for gender, age and weight

Pharmacological or exercise stress echocardiography:

- Severe status unmasked in response to pharmacological stress or exercise, e.g., Increase in peak and mean gradient on pharmacological stress or exercise to within the severe range
- No increase in aortic valve area on pharmacological stress or exercise
- Mean gradient increase >20mmHg during pharmacological stress or exercise

3. Aortic regurgitation

Asymptomatic severe AR

Exercise stress testing:

- Exercise capacity <60% predicted workload for gender, age and weight
- Symptoms unmasked in response to exercise
- Increase in BNP levels on exercise compared with baseline

Exercise stress echocardiography:

- Lack of demonstrated contractile reserve at low workload exercise
- Decrease in LVEF on exercise compared with baseline
- Reduced left ventricular systolic function based on global longitudinal strain on exercise compared with baseline

4. Mitral stenosis

Asymptomatic severe MS

Exercise stress testing:

- Exercise capacity <60% predicted workload for gender, age and weight
- Symptoms unmasked in response to exercise

Symptomatic non-severe MS

	Exercise stress testing: • Exercise capacity <60% predicted workload for gender, age and weight Pharmacological or exercise stress echocardiography: • Severe status unmasked in response to pharmacological stress or exercise, e.g. Increase in mitral valve mean gradient on stress/exercise to severe range – pharmacological stress and exercise • Increase in peak systolic pulmonary artery pressure during low workload exercise to >60 mmHg (SPAP >60 mmHg) – only during exercise
Confounding factors	• Coronary disease • Comorbid lung disease or respiratory insufficiency • Peripheral vascular disease • Arthritis
Outcomes	Indication for intervention based on prognosis for the following without intervention: • Mortality (1 and 5 years) • Hospital attendance/admission for heart failure or unplanned intervention (1 and 5 years) • Reduced cardiac function (echo or CMR parameters – for example LVEF <50% for AS and AR or LVEF <60% for MR) (1 and 5 years) • Symptom onset (for those that were asymptomatic at enrolment in the study) (1 and 5 years) Indication for intervention based on predictors of the following post-operative outcomes and time-points: • Mortality (6 and 12 months) • Hospital attendance for heart failure (6 and 12 months) • Cardiac event-free survival • Reduced cardiac function (echo or CMR parameters – for example LVEF <50%) (6 and 12 months) This may be reported as an adjusted HR, RR or OR. Sensitivity, specificity and AUC will not be included as these do not allow for multivariable adjustment. Use the time point closest to each of the listed endpoints and combine data as follows: 6 months: include 0-6 months 12 months: include >6 months up to 12 months 1 year: include 0-12 months 5 years: include all >1 year. No minimum follow-up.
Study design	• Prospective and retrospective cohort studies that control for confounders in the study design or analysis • Systematic reviews of the above • If no cohort studies are identified case control studies that control for confounders in the study design or analysis will be included but downgraded for risk of bias. This will be assessed separately for each test and population.

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document.

of interest were recorded according to NICE's conflicts of interest policy.

1.1.4 Prognostic evidence

1.1.4.1 Included studies

A search was conducted for prospective and retrospective cohort studies investigating the association of various prognostic factors measured on exercise stress or pharmacological stress testing or echocardiography and outcomes in those that received conservative management of valve disease and those that received surgical treatment of valve disease. The prognostic factors were different depending on the type (e.g. aortic regurgitation or aortic stenosis) and presentation (e.g. asymptomatic severe or symptomatic non-severe valve disease) of valve disease and full details are provided in the protocol.

Nineteen studies (from twenty papers) were included in the review;[6, 9, 21, 32, 36, 51, 72, 122, 124, 132, 152, 155, 157, 160, 166, 171, 195, 204, 230, 231] these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summaries below (Table 3 to Table 15).

This evidence covered the following populations:

- asymptomatic severe aortic stenosis: 9 studies, reported in 10 papers[6, 32, 36, 51, 122, 132, 160, 195, 230, 231]
- symptomatic low-flow aortic stenosis: 3 studies[9, 72, 204]
- asymptomatic severe mitral regurgitation: 5 studies[152, 155, 157, 166, 171]
- symptomatic non-severe mitral regurgitation: 1 study[124]
- heart valve disease in general (rather than a specific type and severity): 1 study[21]

No relevant clinical studies investigating the effects of any of the relevant pre-specified prognostic factors were identified for the following populations: asymptomatic severe aortic regurgitation, asymptomatic severe mitral stenosis and symptomatic non-severe mitral stenosis. Note that to be included, studies had to have performed at least some form of multivariate analysis. Studies that had not included the pre-specified confounders in this multivariate analysis were still considered in the absence of any other evidence that had included these, but they were downgraded for indirectness.

With regards to confounders that were included in the multivariate analysis of studies, studies were not excluded if any of the important confounders pre-specified in the protocol had not been included in the analysis as long as some multivariate analysis had been performed. This was because there was limited available evidence that had accounted for even one of the listed confounders and during protocol development before the review was started it was agreed that the committee did not want studies to be excluded solely on the basis that the multivariate analysis had not included one or all of these confounders. Studies that had not adjusted for the pre-specified confounders were instead downgraded for risk of bias. Studies that only reported univariate results were excluded.

Due to limited available evidence directly matching the protocol, studies that had slightly indirect populations or prognostic factors were included but downgraded for indirectness. For example, some studies that consisted of a mixture of moderate or severe asymptomatic aortic stenosis were included under the 'asymptomatic severe aortic stenosis' group covered in the protocol. Similarly, an example of prognostic factor indirectness that was included in the review was the thresholds used for prognostic factors differing from those pre-specified in

the protocol (e.g. threshold of ≥1 mm for ST segment depression rather than ≥2 mm as specified in the protocol for asymptomatic severe aortic stenosis).

See also the study selection flow chart in Appendix A, study evidence tables in Appendix D, forest plots in Appendix E and GRADE tables in Appendix F.

1.1.4.2 Excluded studies

See the excluded studies list in Appendix J.

1.1.5 Summary of studies included in the prognostic evidence

Table 2: Summary of studies included in the evidence review

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
Asymptomatic severe aortic stenosis						
Amato 2001[6] N=66 Brazil	Asymptomatic severe AS Mean age 49.7 years	Cox proportional hazards regression	Positive exercise test (ST segment depression, precordial chest pain or near syncope, complex ventricular arrhythmia on ECG, failure of systolic BP to rise ≥20 mmHg on exercise)	Age, aortic valve area and exercise testing appear to have been included in the MV analysis.	Appearance of symptoms in daily life or sudden death – mean follow-up 14.77 months Proportional hazards mentioned as analysis but describes results as risk ratio, so has been extracted as a hazard ratio	Risk of bias: very high Indirectness: • prognostic factor – various factors combined rather than individually as in protocol
Capoulade 2014[32] N=157 in severe subgroup Canada, Belgium	Severe asymptomatic AS Mean age 68 years	Cox proportional hazards analysis	Increase of BNP on exercise compared to rest (as continuous variable – assesses effect of higher/lower increases on outcome) - per 100 pg/mL increase from rest	Age, gender, resting mean gradient, resting valvulo-arterial impedance, resting index LA area, resting BNP level and exercise-induced increase in heart rate, mean gradient and	Death or aortic valve replacement indicated by development of symptoms or LV dysfunction – mean follow-up 1.5 years	Risk of bias: very high Indirectness: Prognostic factor – difference between exercise and rest BNP levels as a continuous variable, rather than a dichotomous

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
				valvulo-arterial impedance	Time-to-event data as reported as HR	increase in BNP levels vs. no increase in BNP levels on exercise
Chambers 2019[36] EXTAS study N=305 (moderate or severe AS – N=102 in severe subgroup) UK	Asymptomatic moderate or severe AS Mean age 65 years (moderate or severe AS – 69 years in severe subgroup)	Cox proportional hazards analysis	Abnormal blood pressure response to exercise - sustained fall in systolic BP ≥20 mmHg below the previous stage or baseline level	Age, sex, hypertension, coronary artery disease, abnormal BP response, Doppler stroke volume, mean pressure gradient and rapid early rise in heart rate	Revealed symptoms developing spontaneously or during follow-up (subgroup of 219 moderate or severe AS that remained asymptomatic on baseline exercise) Aortic valve replacement (subgroup of 102 patients with severe AS) - Mean follow-up for the whole cohort was 34.9 months and was not reported separately for the individual severities. Proportional hazards mentioned but reported as an OR, therefore has been extracted as HR	Risk of bias: very high for both outcomes Indirectness: For the revealed symptoms outcome: population – includes moderate or severe AS cases so not limited to asymptomatic severe AS
Das 2005[51]	Asymptomatic AS (mild-	Multivariate logistic regression model	Limiting symptoms on exercise	Variables included in the multivariate	Development of spontaneou	Risk of bias: very high for all three

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
N=125 UK	severe), majority (92%) with moderate or severe disease Mean age 65 years		Abnormal blood pressure response – decrease (≥20 mmHg) or no increase in resting BP on exercise ST depression >2 mm (unclear if coronary disease present)	model: total exercise time, exercise-limiting symptoms, peak transaortic velocity, effective orifice area, abnormal blood pressure response and ST segment depression	s exertional symptoms or CV death – mean follow-up 12 months Not time-to-event as reported as an OR	prognostic factors Indirectness: Population – includes asymptomatic mild to severe AS, but majority are either moderate or severe (92%). Only 42% of the population represented asymptomatic severe AS as specified in the protocol.
Lancellotti 2010-1[122] N=163 Belgium	Asymptomatic moderate or severe AS Mean age 70 years	Cox proportional hazards analysis	Abnormal exercise test (angina; evidence of dyspnoea, dizziness, syncope or near syncope; ≥2 mm ST segment depression relative to baseline; rise in systolic blood pressure during exercise <20 mmHg or a fall in blood pressure; or complex ventricular arrhythmias)	Variables included in the multivariate model: gender; systemic arterial compliance; peak aortic velocity; valvulo-arterial impedance; LV longitudinal strain; LA area index; mitral E wave; mitral E/A ratio; and abnormal exercise test result.	Development of significant symptoms, need for aortic valve replacement or cardiac-related death – mean follow-up 20 months Time-to-event as reported as HR	Risk of bias: very high Indirectness: • Population – includes asymptomatic moderate or severe AS patients • Prognostic factors - combination of various prognostic factors listed in the protocol, rather than providing prognostic information for each one separately
Lancellotti 2010-2[132]	Asymptomatic moderate or severe AS	Cox proportional hazards analysis	Abnormal exercise test (angina; evidence of	Variables included in the multivariate model:	Development of symptoms, need for aortic valve	Risk of bias: very high

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
N=126 Belgium	Mean age 67.5 years		dyspnoea, dizziness, syncope or near syncope; rise in systolic blood pressure during exercise <20 mmHg or a fall in blood pressure; or ventricular tachycardia or >4 premature ventricular complexes in a row)	gender; B-type natriuretic peptide; abnormal response to exercise; aortic valve area; peak aortic velocity; aortic mean pressure gradient; left atrial area index; peak systolic velocity; peak early diastolic annular velocity; peak late diastolic annular velocity; and early diastolic filling/annular velocity.	replacement or cardiac-related death – median follow-up 20.3 months Time-to-event as reported as HR	Indirectness: • Population – includes asymptomatic moderate or severe AS patients • Prognostic factors - combination of various prognostic factors listed in the protocol, rather than providing prognostic information for each one separately
Marechaux 2010[160] N=135 France, Canada, Belgium	Asymptomatic moderate or severe AS – proportion with severe AS unclear Mean age 64 years	Cox proportional hazards model	Increase in mean gradient >20 mmHg during exercise echocardiography	Age ≥65 years, diabetes, rest systolic blood pressure >135 mmHg, LV hypertrophy, rest mean gradient >35 mmHg, increase in mean gradient on exercise >20 mmHg and exercise LV ejection fraction <70%.	Cardiovascular death or need for aortic valve replacement due to symptoms or LV systolic dysfunction – mean follow-up 20 months Time-to-event as reported as a HR	Risk of bias: very high Indirectness: Not limited to asymptomatic severe AS as includes some with asymptomatic moderate AS, with the proportion being unclear.
Peidro 2007[195] N=102 Argentina	Asymptomatic moderate or severe AS – 87% severe	Cox regression	Symptoms on exercise testing Drop in systolic blood pressure	Confounders included in the multivariate analysis is very unclear, but possibly at least the following:	Cardiovascular death or aortic valve replacement – median follow-up	Risk of bias: very high for all three prognostic factors Indirectness:

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
	Mean age 64.35 years		≥10 mmHg on exercise Downsloping ST segment depression >1 mm on exercise (coronary disease not absent in all patients)	symptoms on exercise testing, drop in systolic blood pressure and downsloping ST segment depression >1 mm.	10.7 months Not time-to-event as reported as ORs	• Population – not limited to asymptomatic severe AS as includes some with asymptomatic moderate AS – 87% of the population have severe AS. Drop in systolic BP and ST segment depression: prognostic factor – thresholds used do not match protocol
Singh 2017[231] and Singh 2013[230] N=123 in the severe subgroup (n=174 in total cohort of moderate or severe asymptomatic AS) UK	Severe asymptomatic AS Mean age not given for the severe subgroup, but is 66.2 years for the whole cohort (moderate or severe asymptomatic AS)	Cox proportional hazards regression	Positive exercise test (symptom development as defined in study)	Sex, NT-proBNP, aortic valve area index, cardiac magnetic resonance LV mass/volume ratio, myocardial perfusion reserve and positive exercise tolerance test (strict definition).	Cardiovascular death, typical AS symptoms indicating aortic valve replacement referral or major adverse cardiac events (hospitalisation for heart failure, chest pain, syncope or arrhythmia) – median follow-up 374 days Time-to-event as reported as a HR	Risk of bias: very high Indirectness: None

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
Symptomatic low-flow aortic stenosis						
Annabi 2018[9] TOPAS study N=88 Canada, Austria, Germany, USA	Low-flow low-gradient AS: mean transvalvular pressure gradient <40 mmHg AVA ≤0.6 cm^2/m^2 and LVEF ≤40% At least 40% symptomatic as NYHA class III or IV, but unclear whether remaining proportion symptomatic. Mean age 73 years	Cox proportional hazards analysis	Dobutamine stress echocardiography - increase in mean gradient to >40 mmHg	Age, sex, functional capacity, kidney failure, LVEF at peak dobutamine	Mortality – mean follow-up 4 years Time-to-event data as reported as hazard ratio	Risk of bias: very high Indirectness: • Population – unclear if 60% not in NYHA class III or IV also had symptoms, so may not represent a symptomatic low-flow AS population
Fougeres 2012[72] N=107 France, Belgium	Symptomatic low-flow low-gradient (<40 mmHg) AS. LVEF ≤40%. Median age 76 years	Cox proportional hazards regression models	Pseudo severe AS - AVA increased to ≥1.2 cm^2 with contractile reserve on dobutamine stress testing echocardiography (compares with those with contractile reserve that didn't increase to ≥1.2 cm^2 and those	Logistic EuroSCORE (per 1% increment), baseline mean pressure gradient (per 1 mmHg increment), male gender and pseudo-severe AS	Mortality – median follow-up 25 months Time-to-event as reported as a HR	Risk of bias: high Indirectness: For the multivariate analysis, the no contractile reserve subgroup is combined with true-severe AS and it is unclear whether this group experienced an increase in valve area or not

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
			without contractile reserve)			
Plonska-Gosciniak 2013[204] N=39 Poland, Belgium	Symptomatic low-flow AS (peak gradient ≤45 mmHg and mean gradient ≤35 mmHg). LVEF ≤45%. Small proportion appear to be asymptomatic low-flow AS (12.8% in NYHA class I) Mean age 59 years	Cox proportional hazards regression	No increase in aortic valve area on dobutamine stress testing echocardiography	Confounders included in the multivariate analysis is unclear, but possibly at least the following: aortic valve area at peak stress, absence of aortic valve area increase during stress, absence of contractile reserve and presence of significant coronary artery disease	Death, myocardial infarction or significant worsening of heart failure symptoms (pulmonary oedema) – mean follow-up 353 days Proportional hazards mentioned but reported as an OR, therefore has been extracted as HR	Risk of bias: very high Indirectness: • Population – not limited to symptomatic low-flow AS as appears to include some that are asymptomatic (NYHA class I) – 87% are symptomatic low-flow AS Outcomes – combines medically and surgically treated patients in the same analysis and has not included this as a confounding factor
Asymptomatic severe mitral regurgitation						
Magne 2010[155] N=78 Belgium	Asymptomatic moderate or severe degenerative MR – 60% severe MR Mean age 61 years	Cox proportional hazards model	Exercise pulmonary hypertension (systolic pulmonary artery pressure >60 mmHg) on echocardiography	Age, sex, resting E-wave velocity, exercise left ventricular end-diastolic volume and exercise pulmonary hypertension (SPAP >60 mmHg)	Development of symptoms – mean follow-up 19 months Time-to-event as reported as a HR	Risk of bias: very high Indirectness: Population – not limited to asymptomatic severe MR as includes some with asymptomatic moderate MR. 60% reported to be asymptomatic severe MR.

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
Magne 2014[157] N=115 Belgium, Canada	Asymptomatic moderate or severe primary MR – 63% with severe MR Mean age 61 years	Cox proportional hazards regression model	Absence of contractile reserve (exercise-induced improvement in global longitudinal strain <2%) on echocardiography	Two separate models (one with most variables and another that contained completely different variables) were extracted: • age, sex, exercise regurgitant volume, exercise systolic pulmonary arterial pressure, exercise E/e' ratio, resting BNP level and LV contractile reserve based on global longitudinal strain • LV ejection fraction, LV end-systolic diameter, indexed left atrial volume, pulmonary hypertension and LV contractile reserve based on global longitudinal strain	Cardiac events (cardiovascular death, mitral valve surgery indicated by symptoms or LV dysfunction, or hospitalisation for acute pulmonary oedema or congestive heart failure) – mean follow-up 24 months Time-to-event as reported as a HR	Risk of bias: very high Indirectness: Population – not limited to asymptomatic severe MR as includes some with asymptomatic moderate MR. 63% reported to be asymptomatic severe MR.

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
Magne 2015[152] N=102 Belgium, France, Canada	Asymptomatic or mildly symptomatic moderate or severe degenerative MR – 81% severe and proportion with symptoms unclear Mean age 64 years	Cox proportional hazards regression	Exercise pulmonary hypertension (systolic pulmonary artery pressure >60 mmHg) on echocardiography	Age, sex, LVEF, baseline NYHA class and exercise pulmonary hypertension (SPAP >60 mmHg)	Postoperative cardiovascular events (events (postoperative CV death, CV hospitalisation, stroke or atrial fibrillation) – mean follow-up 50 months Time-to-event as reported as a HR	Risk of bias: very high Indirectness: Population – not limited to asymptomatic severe MR as includes some with asymptomatic moderate MR. 81% reported to be asymptomatic severe MR. Also unclear proportion has mild symptoms.
Messika-Zeitoun 2006[166] N=134 USA	Asymptomatic moderate or severe organic mitral regurgitation – 57% with severe MR Mean age 63 years	Cox proportional hazards model	Functional capacity (peak VO2) on exercise ≤84% of predicted for age, weight and gender	Age, effective regurgitant orifice, gender, LV ejection fraction and reduced functional capacity on exercise (peak VO2 ≤84%).	Clinical events (death, heart failure or new severe symptoms, or new atrial arrhythmia) or indication for surgery – mean follow-up 2.2 years Proportional hazards mentioned but reported as a RR, therefore has been extracted as HR	Risk of bias: very high Indirectness: • Population – not limited to asymptomatic severe MR as includes some with asymptomatic moderate MR. 57% reported to be asymptomatic severe MR. Prognostic factor – threshold of <60% in protocol for exercise capacity but threshold of 84% used in this study
Moss 2014[171]	Asymptomatic/mildly	Cox proportion	Absence of contractile	Age, baseline LV	All-cause mortality or	Risk of bias: very high

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
N=125 Thailand	symptomatic moderate-severe or severe functional MR – 81% severe MR. Also includes ~18% that were symptomatic, in NYHA class III or IV Mean age 60 years	al hazards model	reserve (improvement in global left ventricular function of <10% compared to baseline) value on dobutamine stress echocardiography testing	ejection fraction, NYHA class, moderate/severe tricuspid regurgitation and presence/absence of contractile reserve.	requirement for heart transplant – median follow-up 62 months Time-to-event as reported as a HR	Indirectness: • Population – not limited to asymptomatic severe MR as includes some with moderate-severe disease, and also some with mild symptoms (proportion unclear). In addition, ~18% are reported to be symptomatic and in NYHA classes III or IV. Outcomes – have not provided results separately for those receiving medical management only and those that received surgery and no adjustment in MV analysis
Symptomatic non-severe mitral regurgitation						
Lancellotti 2005[124] N=161 Belgium	Symptomatic non-severe MR (functional MR secondary to heart failure) – includes mild-severe	Cox proportional hazards regression	Increase in effective regurgitant orifice area by ≥13 mm^2 (severe status unmasked in response to exercise) on	ERO increase ≥13 mm^2 on exercise, ERO ≥20 mm^2 at rest and trans-tricuspid pressure gradient difference	Cardiac death – mean follow-up 35 months Hospital admission for heart failure – mean	Risk of bias: very high Indirectness: • Population – ~32% had symptomatic severe MR rather

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
	MR, with ~32% having severe MR at rest. Mean age 65 years		echocardiography	(cardiac death outcomes) ERO increase ≥13 mm^2 on exercise, trans-tricuspid pressure gradient difference and LV end-systolic volume at rest (hospital admission for heart failure outcome)	follow-up 35 months Time-to-event as reported as a HR	than symptomatic non-severe MR at rest. Prognostic factor – ERO increase of ≥13 mm^2 may not represent increase to severe range in all patients, particularly in very mild cases of MR at rest.
Various types of valve disease combined						
Bhattacharyya 2013[21] N=100 UK	Various types of valve disease, reported together as one single group: Asymptomatic severe and symptomatic non-severe MR and MS, asymptomatic severe AS (including low-flow AS) and asymptomatic severe AR Mean age 67.26 years	Cox regression analysis	Positive stress test (defined differently for each different population included)	MV analysis appears to have been performed as 'independent predictors' mentioned, but confounders adjusted for unclear	Admission for worsening HF or death – median follow-up 12.6 months Time-to-event as reported as a HR	Risk of bias: very high Indirectness: • Population – different types of HVD combined • Prognostic factor – multiple different factors in our protocol combined together rather than reported separately • Outcomes – medically and surgically managed patients combined rather than

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
						presenting results separately

See Appendix D for full evidence tables.

1.1.6 Summary of the prognostic evidence

Asymptomatic severe AS

Table 3: Clinical evidence summary: positive exercise test (various definitions qualify)

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Risk of bias	Imprecision	Indirectness	GRADE Quality
Positive exercise test[a] vs. negative exercise test for predicting symptoms in daily life or sudden death Follow-up: mean 14.77 months (asymptomatic severe AS; mean age 49.7 years; medically managed)	1 (n=66)	Adjusted HR: 7.60 (2.34 to 24.63)[b]	Very serious[c]	None	Serious[d]	VERY LOW
Abnormal exercise test[e] vs. normal exercise test for predicting development of significant symptoms, need for aortic valve replacement or cardiac-related death Follow-up: mean 20 months (asymptomatic moderate or severe AS; mean age 70 years; medically managed and censored at cardiac surgery)	1 (n=163)	Adjusted HR: 1.10 (0.60 to 2.0)[f]	Very serious[c]	Very serious[g]	Serious[h]	VERY LOW
Abnormal exercise test[i] vs. normal exercise test for predicting development of symptoms, need for aortic valve replacement or cardiac-related death Follow-up: median 20.3 months (asymptomatic moderate or severe AS; mean age 67.5 years;	1 (n=126)	Adjusted HR: 0.95 (0.49 to 1.80)[j]	Very serious[c]	Very serious[g]	Serious[h]	VERY LOW

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Risk of bias	Imprecision	Indirectness	GRADE Quality
medically managed and censored at cardiac surgery)						

(a) Positive exercise test defined as: horizontal or downsloping ST segment depression of ≥1 mm in men or ≥2 mm in women, or an upsloping ST segment depression of ≥3 mm in men, measured 0.08 seconds after the J point (upsloping ST segment depression in women was considered negative); symptoms of aortic stenosis (precordial chest pain or near syncope); complex ventricular arrhythmia on ECG; or no rise in systolic blood pressure by ≥20 mmHg compared with baseline.

(b) Methods: multivariable analysis, not including key confounders in protocol but adjusted for the following: age, aortic valve area and exercise testing.

(c) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

(d) Prognostic factor indirectness – combination of various prognostic factors listed in the protocol, rather than providing prognostic information for each one separately (symptoms on exercise, reduction in BP >20 mmHg, ST depression and complex ventricular arrhythmia)

(e) The test was considered abnormal if patients presented with any of the following: angina; evidence of dyspnoea, dizziness, syncope or near syncope; ≥2 mm ST segment depression relative to baseline; rise in systolic blood pressure during exercise <20 mmHg or a fall in blood pressure; or complex ventricular arrhythmias.

(f) Methods: multivariable analysis, not including key confounders in protocol but adjusted for the following: gender; systemic arterial compliance; peak aortic velocity; valvulo-arterial impedance; LV longitudinal strain; LA area index; mitral E wave; mitral E/A ratio; and abnormal exercise test result.

(g) 95% Cis cross null line and are very wide

(h) Population indirectness – not limited to asymptomatic severe AS as includes some with asymptomatic moderate AS; prognostic factor indirectness – combination of various prognostic factors listed in the protocol, rather than providing prognostic information for each one separately

(i) The test was considered abnormal if patients presented with any of the following: angina; evidence of dyspnoea, dizziness, syncope or near syncope; rise in systolic blood pressure during exercise <20 mmHg or a fall in blood pressure; or ventricular tachycardia or >4 premature ventricular complexes in a row.

(j) Methods: multivariable analysis, not including key confounders in protocol but adjusted for the following: gender; B-type natriuretic peptide; abnormal response to exercise; aortic valve area; peak aortic velocity; aortic mean pressure gradient; left atrial area index; peak systolic velocity; peak early diastolic annular velocity; peak late diastolic annular velocity; and early diastolic filling/annular velocity.

Table 4: Clinical evidence summary: symptoms unmasked in response to exercise

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Risk of bias	Imprecision	Indirectness	GRADE Quality
Symptom-positive[a] vs. symptom-negative on exercise for predicting cardiovascular death, typical AS symptoms indicating AVR referral or major adverse cardiac events (hospitalisation for heart failure, chest pain, syncope or arrhythmia) Follow-up: median 374 days (asymptomatic severe AS; mean age for severe subgroup unclear, but is 66.2 years for whole cohort including moderate or severe	1 (n=123)	Adjusted HR: 2.94 (1.29 to 6.70)[b]	Very serious[c]	None	None	LOW

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Risk of bias	Imprecision	Indirectness	GRADE Quality
cases; medically managed as indication for AVR captured as part of the outcome)						
Limiting symptoms[d] vs. no limiting symptoms on exercise for predicting development of spontaneous exertional symptoms or cardiovascular death Follow-up: mean 12 months (asymptomatic mild-severe AS, with majority being moderate or severe disease; mean age 65.0 years; medically managed – not explicitly stated but no mention of any aortic valve operations being performed)	1 (n=125)	Adjusted OR: 7.73 (2.79 to 21.39)[e]	Very serious[c]	None	Serious[f]	VERY LOW
Symptoms[g] vs. no symptoms on exercise for predicting cardiovascular death or aortic valve replacement Follow-up: median 10.7 months. (asymptomatic moderate or severe AS; mean age 64.35 years; medically managed as aortic valve replacement captured as part of the outcome)	1 (n=102)	Adjusted OR: 2.48 (1.32 to 4.66)[h]	Very serious[c]	None	Serious[i]	VERY LOW

(a) Symptom-positive on exercise testing was defined in the study as the following: if the patient stopped prematurely due to limiting breathlessness or dizziness at <80% of their predicted workload or chest pain at any stage

(b) Methods: multivariable analysis, not including key confounders in protocol but adjusted for the following: sex, NT-proBNP, aortic valve area index, cardiac magnetic resonance LV mass/volume ratio, myocardial perfusion reserve and positive exercise tolerance test

(c) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

(d) Limiting symptoms defined as follows: limiting breathlessness/chest discomfort or dizziness

(e) Methods: multivariable analysis, not including any of the key confounders in the protocol. However, one of the pre-specified confounders (lung disease) was an exclusion criterion for the study. The following variables were adjusted for: total exercise time, exercise-limiting symptoms, peak transaortic velocity, effective orifice area, abnormal blood pressure response and ST segment depression.

(f) Population indirectness – includes asymptomatic mild to severe AS, but majority are either moderate or severe (92%). Only 42% of the population represented asymptomatic severe AS as specified in the protocol.

(g) Symptoms defined as follows: angor, syncope or presyncope, or dyspnoea

(h) Methods: multivariable analysis, but unclear which variables included in the analysis. One of the confounders listed in the protocol was an exclusion criterion (lung disease) and the remaining were not mentioned. The following variables may have been adjusted for in the multivariate model, but this is very unclear: symptoms on exercise testing, drop in systolic blood pressure and downsloping ST segment depression >1 mm.

(i) Population indirectness – not limited to asymptomatic severe AS as includes some with asymptomatic moderate AS – 87% of the population have severe AS.

Table 5: Clinical evidence summary: absolute difference of BNP levels from rest to exercise (per 100 pg/ml increase from rest)

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Risk of bias	Imprecision	Indirectness	GRADE Quality
Absolute difference of BNP levels from rest to exercise (per 100 pg/ml increase from rest) as a continuous measure for predicting death or aortic valve replacement indicated by symptom development or LV dysfunction Follow-up mean 1.5 years. (asymptomatic severe AS; mean age 68.0 years; medically managed as AVR captured as part of the outcome)	1 (n=157)	Adjusted HR: 3.40 (2.20 to 5.23)[a]	Very serious[b]	None	Serious[c]	VERY LOW

(a) Methods: multivariable analysis, not including key confounders in protocol but adjusted for the following: age, gender, resting mean gradient, resting valvulo-arterial impedance, resting indexed left atrial area, resting BNP level and exercise-induced increases in heart rate, mean gradient and valvulo-arterial impedance

(b) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

(c) Prognostic factor indirectness – difference between exercise and rest BNP levels as a continuous variable, rather than a dichotomous increase in BNP levels vs. no increase in BNP levels on exercise compared with rest

Table 6: Clinical evidence summary: abnormal response of blood pressure to exercise

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Risk of bias	Imprecision	Indirectness	GRADE Quality
Abnormal (reduction or no increase in BP compared with rest) vs. normal blood pressure response to exercise for predicting cardiovascular death or development of spontaneous exertional symptoms Follow-up: mean 12 months (asymptomatic mild-severe AS, with majority being moderate or severe disease; mean age 65.0 years; medically managed – not explicitly stated but no mention of any aortic valve operations being performed)	1 (n=125)	Adjusted OR: 1.02 (0.99 to 1.06)[a]	Very serious[b]	Serious[c]	Serious[d]	VERY LOW

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Risk of bias	Imprecision	Indirectness	GRADE Quality
Drop in systolic blood pressure ≥10 mmHg vs. <10 mmHg on exercise compared to rest for predicting cardiovascular death or aortic valve replacement Follow-up: mean 10.7 months (asymptomatic moderate or severe AS; mean age 64.35 years; medically managed as aortic valve replacement captured as part of the outcome)	1 (n=102)	Adjusted OR: 1.95 (1.00 to 3.81)[e]	Very serious[b]	Serious[c]	Serious[f]	VERY LOW
Abnormal (sustained reduction of systolic BP ≥20 mmHg below previous stage or baseline level) vs. normal blood pressure response to exercise for predicting revealed symptoms developing spontaneously or during follow-up Follow-up for the whole cohort: mean 34.9 (34.6) months. (asymptomatic moderate or severe AS patients that remained asymptomatic on the baseline exercise test; mean age of the subgroup unclear but 65.0 years for whole cohort; medically managed as no indication for AVR unless symptoms developed)	1 (n=219 in subgroup analysed)	Adjusted HR: 1.87 (0.92 to 3.79)[g]	Very serious[b]	Serious[c]	Serious[h]	VERY LOW
Abnormal (sustained reduction of systolic BP ≥20 mmHg below previous stage or baseline level) vs. normal blood pressure response to exercise for predicting aortic valve replacement during follow-up Follow-up for the whole cohort: mean 34.9 (34.6) months. (asymptomatic severe AS patients; mean age 69.0 years; medically managed up until indication for developed)	1 (n=102 in severe subgroup analysed)	Adjusted HR: 1.86 (1.01 to 3.44)[a]	Very serious[b]	None	None	LOW

(a) *Methods: multivariable analysis, not including any of the key confounders in the protocol. However, one of the pre-specified confounders (lung disease) was an exclusion criterion for the study. The following variables were adjusted for: total exercise time, exercise-limiting symptoms, peak transaortic velocity, effective orifice area, abnormal blood pressure response and ST segment depression.*

(b) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
(c) C95% CIs cross the null line
(d) Population indirectness – includes asymptomatic mild to severe AS, but majority are either moderate or severe (92%). Only 42% of the population represented asymptomatic severe AS as specified in the protocol.
(e) Methods: multivariable analysis, but unclear which variables included in the analysis. One of the confounders listed in the protocol was an exclusion criterion (lung disease) and the remaining were not mentioned. The following variables may have been adjusted for in the multivariate model, but this is very unclear: symptoms on exercise testing, drop in systolic blood pressure and downsloping ST segment depression >1 mm.
(f) Population indirectness – not limited to asymptomatic severe AS as includes some with asymptomatic moderate AS – 87% of the population have severe AS. Prognostic factor indirectness – threshold used in study differs to that specified in protocol, as ≥10 mmHg drop in systolic blood pressure on exercise is used rather than ≥20 mmHg drop on exercise.
(g) Methods: multivariable analysis, including one of the key confounders in the protocol (coronary artery disease). Two other confounders listed in the protocol were exclusion criteria and the remaining one was not mentioned. The following variables were adjusted for: rapid early rise in heart rate, age, sex, hypertension, Doppler stroke volume, mean pressure gradient, abnormal blood pressure response and coronary artery disease
(h) Population indirectness – includes moderate or severe AS patients that were asymptomatic at baseline and remained asymptomatic on baseline exercise testing, not limited to asymptomatic severe AS

Table 7: Clinical evidence summary: ST segment depression on exercise

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Risk of bias	Imprecision	Indirectness	GRADE Quality
ST depression ≥2 mm vs. <2 mm on exercise for predicting development of spontaneous exertional symptoms or cardiovascular death Follow-up: mean 12 months. (asymptomatic mild-severe AS, with majority being moderate or severe disease; mean age 65.0 years; medically managed – not explicitly stated but no mention of any aortic valve operations being performed)	1 (n=125)	Adjusted OR: 0.97 (0.94 to 1.01)[a]	Very serious[b]	Serious	Serious[c]	VERY LOW
Downsloping ST segment depression >1 mm vs. ≤1 mm on exercise for predicting cardiovascular death or aortic valve replacement Follow-up median 10.7 months (asymptomatic moderate or severe AS; mean age 64.35 years; medically managed as aortic valve replacement captured as part of the outcome)	1 (n=102)	Adjusted OR: 1.89 (1.03 to 3.47)[d]	Very serious[b]	None	Serious[e]	VERY LOW

(a) Methods: multivariable analysis, not including any of the key confounders in the protocol. However, one of the pre-specified confounders (lung disease) was an exclusion criterion for the study. The following variables were adjusted for: total exercise time, exercise-limiting symptoms, peak transaortic velocity, effective orifice area, abnormal blood pressure response and ST segment depression.

(b) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

(c) Population indirectness – includes asymptomatic mild to severe AS, but majority are either moderate or severe (92%). Only 42% of the population represented asymptomatic severe AS as specified in the protocol. Prognostic factor indirectness – unclear if coronary disease is absent, which was specified in the protocol as important when this prognostic factor was used.

(d) Methods: multivariable analysis, but unclear which variables included in the analysis. One of the confounders listed in the protocol was an exclusion criterion (lung disease) and the remaining were not mentioned. The following variables may have been adjusted for in the multivariate model, but this is very unclear: symptoms on exercise testing, drop in systolic blood pressure and downsloping ST segment depression >1 mm.

(e) Population indirectness - not limited to asymptomatic severe AS as includes some with asymptomatic moderate AS – 87% of the population have severe AS. Prognostic factor indirectness – threshold used in study differs to that specified in protocol, as >1 mmHg ST segment depression on exercise is used rather than >2 mm ST segment depression on exercise. Coronary disease is also not absent in all patients, which was specified in the protocol as important when interpreting this prognostic factor. The study states that ST segment depression >1 mm did not identify those patients with associated coronary disease.

Table 8: Clinical evidence summary: mean gradient increase >20 mmHg on echocardiography during exercise

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Risk of bias	Imprecision	Indirectness	GRADE Quality
Increase in mean gradient >20 mmHg vs. ≤20 mmHg for predicting cardiovascular death or need for aortic valve replacement due to symptoms or LV systolic dysfunction Follow-up mean 20 months. (asymptomatic/minimally symptomatic moderate or severe AS; mean age 64.0 years; medically managed as AVR captured as part of the outcome)	1 (n=135)	Adjusted HR: 3.83 (2.18 to 6.73)[a]	Very serious[b]	None	Serious[c]	VERY LOW

(a) Methods: multivariable analysis, not including any of the key confounders in the protocol. However, two of the confounders listed in the protocol were exclusion criteria for the study (coronary artery disease and lung disease). The variables including in the analysis were unclear, but the HR appears to have been adjusted for the following: age ≥65 years, diabetes, rest systolic blood pressure >135 mmHg, LV hypertrophy, rest mean gradient >35 mmHg, increase in mean gradient on exercise >20 mmHg and exercise LV ejection fraction <70%.

(b) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

(c) Population indirectness – not limited to asymptomatic severe AS but includes some with asymptomatic moderate AS, the proportion of which is unclear

Symptomatic low-flow AS

Table 9: Clinical evidence summary: no increase in valve area on dobutamine stress echocardiography testing

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Risk of bias	Imprecision	Indirectness	GRADE Quality
No increase in valve area to >1.2 cm^2 (true-severe AS or those with no contractile reserve) vs. increase in valve area to >1.2 cm^2 (pseudo-severe AS) on dobutamine stress testing for predicting overall mortality Follow-up: median 25 months (symptomatic low-flow aortic stenosis; median age 76.0 years; patients managed conservatively for >6 months)	1 (n=107)	Adjusted HR: 1.89 (1.33 to 2.69)[a]	Serious[b]	None	Serious[c]	LOW
No increase in valve area vs. increase in valve area on dobutamine stress testing for predicting death, myocardial infarction or significant worsening of heart failure symptoms (pulmonary oedema) Follow-up: mean 353 days (symptomatic low-flow aortic stenosis, ~12.8% appear to be asymptomatic as are in NYHA class I; mean age 59.0 years; includes patients that were managed medically or surgically and does not include this as a confounder to adjust for in the MV analysis)	1 (n=39)	Adjusted HR: 5.70 (2.02 to 16.12)[d]	Very serious[b]	None	Serious[e]	VERY LOW

(a) Methods: multivariable analysis, not including any of the key confounders in the protocol. The variables included in the analysis were: pseudo-severe AS, logistic EuroSCORE, baseline mean pressure gradient and male sex.

(b) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

(c) Prognostic factor indirectness – in the subgroup with no contractile reserve it was not possible to determine whether it was true-severe AS or pseudo-severe AS based on increase/no increase in valve area and the study reports them as a separate, third group. However, for the multivariate analysis the no contractile reserve subgroup is combined with true-severe AS and it is unclear whether this group experienced an increase in valve area or not. Based on study characteristics table, only small increases in valve area reported in the no contractile reserve group so may all have shown no increase as well as in the true-severe AS group, though this is unclear.

(d) Methods: multivariable analysis, though confounders included in the reported multivariate analysis are unclear. May have included the following: aortic valve area at peak stress, absence of aortic valve area increase during stress, absence of contractile reserve and presence of significant coronary artery disease. If these were the included confounders, only one of those specified in the protocol has been included.

(e) Population indirectness – not limited to symptomatic low-flow AS as appears to include some that are asymptomatic (NYHA class I) – 87% are symptomatic low-flow AS. Outcome indirectness – combines medically and surgically treated

patients in the same analysis and has not included this as a confounding factor, whereas in the protocol ideally separate results for those medically and surgically treated could be extracted

Table 10: Clinical evidence summary: increase of mean gradient to within severe range on dobutamine stress echocardiography testing

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Risk of bias	Imprecision	Indirectness	GRADE Quality
Increase in mean gradient to within severe range (≥40 mmHg) vs. no increase to severe range (<40 mmHg) for predicting mortality Follow-up: mean 4 years (Low-flow low-gradient aortic stenosis, at least 40% symptomatic as NYHA class III or IV but unclear if remaining patients were symptomatic; mean age 73.0 years; medically managed subgroup)	1 (n=88)	Adjusted HR: 0.93 (0.21 to 4.07)[a]	Very serious[b]	Very serious[c]	Serious[d]	VERY LOW

(a) Methods: multivariable analysis, not including any of the key confounders in the protocol. The variables included in the analysis were: age, sex, functional capacity (Duke activity status index), kidney failure and LVEF at peak dobutamine stress.
(b) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
(c) 95% CIs cross the null line and intervals are very wide
(d) Population indirectness – unclear if 60% not in NYHA class III or IV also had symptoms, so may not represent a symptomatic low-flow AS population specified in the protocol as may include some asymptomatic low-flow patients.

Asymptomatic severe MR

Table 11: Clinical evidence summary: exercise capacity (VO_2 max) ≤84% predicted for weight, age and gender

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Risk of bias	Imprecision	Indirectness	GRADE Quality
Exercise capacity (VO_2 max) ≤84% vs. >84% predicted for weight, age and gender for predicting clinical events (death, heart failure or new severe symptoms, or new atrial arrhythmia) or indication for surgery Follow-up: mean 2.2 years.	1 (n=134)	Adjusted HR: 1.53 (1.11 to 2.11)[a]	Very serious[b]	None	Serious[c]	VERY LOW

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Risk of bias	Imprecision	Indirectness	GRADE Quality
(Asymptomatic moderate or severe organic mitral regurgitation, 57% with severe MR; mean age 63.0 years; medically managed as surgery indication captured as part of the outcome)						

(a) Methods: multivariable analysis, not including any of the key confounders in the protocol. Moderate or severe lung disease was an exclusion criterion for the study, but the other three confounders listed in the protocol were not mentioned. The variables included in the analysis were: age, effective regurgitant orifice, gender, LV ejection fraction and reduced functional capacity on exercise (peak VO2 ≤84%).

(b) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

(c) Population indirectness – not limited to asymptomatic severe MR but includes some with asymptomatic moderate MR. 57% reported to be asymptomatic severe MR. Prognostic factor indirectness – threshold of <60% in protocol for exercise capacity but threshold of 84% used in this study.

Table 12: Clinical evidence summary: increase of systolic pulmonary artery pressure to >60 mmHg on exercise echocardiography testing

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Risk of bias	Imprecision	Indirectness	GRADE Quality
Systolic pulmonary artery pressure >60 mmHg (exercise pulmonary hypertension) vs. ≤60 mmHg for predicting development of symptoms during follow-up[a] Follow-up: mean 19 months. (Asymptomatic moderate or severe mitral regurgitation – 60% with severe disease; mean age 61.0 years; medically managed as symptom development was indication for operation)	1 (n=78)	Adjusted HR: 2.10 (1.41 to 3.12)[b]	Very serious[c]	None	Serious[d]	VERY LOW
Systolic pulmonary artery pressure >60 mmHg (exercise pulmonary hypertension) vs. ≤60 mmHg for predicting postoperative cardiovascular events (postoperative cardiovascular death, cardiovascular hospitalisation, stroke or atrial fibrillation Follow-up: mean 50 months (Asymptomatic or mildly symptomatic moderate or severe	1 (n=102)	Adjusted HR: 2.00 (1.06 to 3.79)[e]	Very serious[c]	None	Serious[f]	VERY LOW

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Risk of bias	Imprecision	Indirectness	GRADE Quality
mitral regurgitation – 81% severe, proportion mildly symptomatic unclear; mean age 64.0 years; surgically managed)						

(a) Symptoms during follow-up were defined as any of the following: shortness of breath, angina, dizziness or syncope with exertion.

(b) Methods: multivariable analysis, not including any of the key confounders in the protocol. The variables included in the analysis were: age, sex, resting E-wave velocity, exercise left ventricular end-diastolic volume and exercise pulmonary hypertension (SPAP >60 mmHg).

(c) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

(d) Population indirectness – not limited to asymptomatic severe MR but includes some with asymptomatic moderate MR. 60% reported to be asymptomatic severe MR.

(e) Methods: multivariable analysis, not including any of the key confounders in the protocol. Though suspected coronary artery disease was an exclusion criterion, some did have concomitant coronary artery bypass grafting performed with valve intervention. The variables included in the analysis were: age, sex, LVEF, baseline NYHA class and exercise pulmonary hypertension (SPAP >60 mmHg)

(f) Population indirectness – not limited to asymptomatic severe MR but includes some with asymptomatic moderate MR. 81% reported to be asymptomatic severe MR. Also includes asymptomatic or minimally symptomatic patients, and unclear proportion within each of these groups.

Table 13: Clinical evidence summary: lack of contractile reserve on stress echocardiography testing

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Risk of bias	Imprecision	Indirectness	GRADE Quality
Absence (<2% improvement in GLS) vs. presence (≥2% improvement in GLS) of contractile reserve on exercise for predicting cardiac events (cardiovascular death, mitral valve surgery indicated by symptoms of LV dysfunction or hospitalisation for acute pulmonary oedema or congestive heart failure) Follow-up: mean 24 months (Asymptomatic moderate or severe primary mitral regurgitation, 63% severe; mean age 61.0 years; medically managed as valve surgery captured as part of the outcome)	1 (n=115)	Adjusted HR: 2.27 (1.07 to 4.83)[a]	Very serious[b]	None	Serious[c]	VERY LOW
		Adjusted HR: 1.60 (1.11 to 2.31)[d]	Very serious[b]	None	Serious[c]	VERY LOW
Absence (<10% improvement in global left ventricular function on dobutamine testing) vs. presence (≥10%	1 (n=125)	Adjusted HR: 2.94 (1.31 to 6.61)[e]	Very serious[b]	None	Serious[f]	VERY LOW

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Risk of bias	Imprecision	Indirectness	GRADE Quality
improvement in global left ventricular function on dobutamine testing) of contractile reserve on dobutamine testing for all-cause mortality or requirement for heart transplant Follow-up: median 62 months (Asymptomatic/mildly symptomatic moderate-severe or severe functional mitral regurgitation, 81% with severe disease and ~18% that were symptomatic in NYHA class III or IV; mean age 60.0 years; medically or surgically managed combined and not included in MV analysis)						

(a) *Methods: multivariable analysis, not including any of the key confounders in the protocol. Coronary artery disease was an exclusion criterion but the other prespecified confounders in the protocol were not adjusted for. The variables included in the analysis were: age, sex, exercise regurgitant volume, exercise systolic pulmonary arterial pressure, exercise E/e' ratio, resting BNP level and LV contractile reserve based on global longitudinal strain (exercise-induced improvement in global longitudinal strain ≥2%).*

(b) *Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias*

(c) *Population indirectness – not limited to asymptomatic severe MR as includes some with asymptomatic moderate MR. 63% reported to be asymptomatic severe MR.*

(d) *Methods: multivariable analysis, not including any of the key confounders in the protocol. Coronary artery disease was an exclusion criterion but the other prespecified confounders in the protocol were not adjusted for. The variables included in the analysis were: LV ejection fraction, LV end-systolic diameter, indexed left atrial volume, pulmonary hypertension and LV contractile reserve based on global longitudinal strain (exercise-induced improvement in global longitudinal strain ≥2%).*

(e) *Methods: multivariable analysis, not including any of the key confounders in the protocol. The variables included in the analysis were: age, baseline LV ejection fraction, NYHA class, moderate/severe tricuspid regurgitation and presence/absence of contractile reserve.*

(f) *Population indirectness – not limited to asymptomatic severe MR as includes some with moderate-severe disease, and also some with mild symptoms (proportion unclear). In addition, ~18% are reported to be symptomatic and in NYHA classes III or IV. Outcome indirectness – have not provided results separately for those receiving medical management only and those that received surgery during follow-up as set out in the protocol. In addition, adjustment for surgery has not been included in the multivariate analysis.*

Symptomatic non-severe MR

Table 14: Clinical evidence summary: severe status unmasked on exercise echocardiography (increase of effective regurgitant orifice area by ≥13 mm^2) in response to exercise

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Risk of bias	Imprecision	Indirectness	GRADE Quality
Increase of effective regurgitant orifice area by ≥13 mm^2 vs. <13 mm^2 for predicting cardiac death Follow-up: mean 35 months. (Symptomatic non-severe functional mitral regurgitation, includes mild-severe MR with ~32% having severe MR at rest; mean age 65.0 years; medically managed as patients censored from analysis if surgery performed)	1 (n=161)	Adjusted HR: 5.00 (1.91 to 13.8)[a]	Very serious[b]	None	Serious[c]	VERY LOW
Increase of effective regurgitant orifice area by ≥13 mm^2 vs. <13 mm^2 for predicting hospital admission for heart failure Follow-up: mean 35 months. (Symptomatic non-severe functional mitral regurgitation, includes mild-severe MR with ~32% having severe MR at rest; mean age 65.0 years; medically managed as patients censored from analysis if surgery performed)	1 (n=161)	Adjusted HR: 3.60 (1.40 to 9.20)[d]	Very serious[b]	None	Serious[c]	VERY LOW

(a) Methods: multivariable analysis, not including any of the key confounders in the protocol. The variables included in the analysis were: ERO increase ≥13 mm^2 on exercise, ERO ≥20 mm^2 at rest and transtricuspid pressure gradient difference

(b) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

(c) Population indirectness – ~32% had symptomatic severe MR rather than symptomatic non-severe (mild or moderate) MR at rest. Therefore, some with increase of ERO ≥13 may have already been within the severe range. Mean ERO at rest is consistent with non-severe MR as <20 mm^2. Prognostic factor indirectness – ERO increase of ≥13 mm^2 may not represent increase to severe range in all patients, particularly in very mild cases of MR at rest.

(d) Methods: multivariable analysis, not including any of the key confounders in the protocol. The variables included in the analysis were: ERO increase ≥13 mm^2 on exercise, transtricuspid pressure gradient difference and LV end-systolic volume at rest

Any valve disease combined

Table 15: Clinical evidence summary: positive exercise echocardiogram (different definitions for each presentation of valve disease)

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Risk of bias	Imprecision	Indirectness	GRADE Quality
Positive vs. negative exercise echocardiogram[a] for predicting admission for worsening heart failure or death Follow-up median 12.6 months. (Various valve disease presentations – symptomatic non-severe mitral regurgitation, asymptomatic severe mitral regurgitation, symptomatic non-severe mitral stenosis, asymptomatic severe mitral stenosis, asymptomatic severe aortic stenosis and asymptomatic severe aortic regurgitation; mean age 67.26 years; medically or surgically managed patients included, does not appear to have adjusted for surgery)	1 (n=100)	Adjusted HR: 15.49 (4.18 to 57.40)[b]	Very serious[c]	None	Serious[d]	VERY LOW

(a) A positive echocardiogram was defined as follows for the different valve disease presentations: Symptomatic non-severe MR, increase in severity to severe – effective orifice area ≥0.4 cm² (organic) or ≥0.2 cm² (functional); asymptomatic severe MR, increase in pulmonary artery systolic pressure >60 mmHg; symptomatic non-severe MS, increase in mean transmitral gradient ≥15 mmHg or estimated pulmonary artery systolic pressure ≥60 mmHg; asymptomatic severe MS, increase in mean transmitral gradient ≥15 mmHg or estimated pulmonary artery systolic pressure ≥60 mmHg or symptom development; asymptomatic severe AS, increase in mean transaortic gradient ≥20 mmHg; and asymptomatic severe AR, lack of increase in LVEF ≥5% or exercise-induced reduction in LVEF.

(b) Methods: multivariable analysis appears to have been performed as the study mentions independent predictors, however the variables included in the analysis are unclear.

(c) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

(d) Population indirectness – different valve disease presentation types combined as a single group rather than presenting separately as in protocol. Prognostic factor indirectness – various factors listed in protocol combined under positive exercise echocardiogram rather than being reported separately.

See Appendix F for full GRADE tables.

1.1.7 Economic evidence

1.1.7.1 Included studies

No health economic studies were included.

1.1.7.2 Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

1 See also the health economic study selection flow chart in Appendix G.

1.1.9 Economic model

This area was not prioritised for new cost-effectiveness analysis.

1.1.10 Unit costs

Relevant unit costs are provided below to aid consideration of cost effectiveness.

Resource	Unit costs	Source
Electrocardiogram Monitoring or Stress Testing	£179 (a)	NHS reference costs 2018/19[179]
Complex Echocardiogram	£375 (b)	NHS reference costs 2018/19[179]

Source: Costs obtained from the NHS reference cost 2018/19
(a) Cost obtained for outpatients
(b) Complex echocardiogram (stress echocardiogram)

1.1.11 Evidence statements

Effectiveness

See the summary of evidence in Table 3, Table 5, Table 6, Table 4, Table 7, Table 8,

Table **9: Clinical evidence summary: no increase in valve area on dobutamine stress echocardiography testing**

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Risk of bias	Imprecision	Indirectness	GRADE Quality
No increase in valve area to >1.2 cm^2 (true-severe AS or those with no contractile reserve) vs. increase in valve area to >1.2 cm^2 (pseudo-severe AS) on dobutamine stress testing for predicting overall mortality Follow-up: median 25 months (symptomatic low-flow aortic stenosis; median age 76.0 years; patients managed conservatively for >6 months)	1 (n=107)	Adjusted HR: 1.89 (1.33 to 2.69)[a]	Serious[b]	None	Serious[c]	LOW
No increase in valve area vs. increase in valve area on dobutamine stress testing for predicting death, myocardial infarction or significant worsening of heart failure symptoms (pulmonary oedema) Follow-up: mean 353 days (symptomatic low-flow aortic stenosis, ~12.8% appear to be asymptomatic as are in NYHA class I; mean age 59.0 years; includes patients that were	1 (n=39)	Adjusted HR: 5.70 (2.02 to 16.12)[d]	Very serious[b]	None	Serious[e]	VERY LOW

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Risk of bias	Imprecision	Indirectness	GRADE Quality
managed medically or surgically and does not include this as a confounder to adjust for in the MV analysis)						

(f) Methods: multivariable analysis, not including any of the key confounders in the protocol. The variables included in the analysis were: pseudo-severe AS, logistic EuroSCORE, baseline mean pressure gradient and male sex.

(g) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

(h) Prognostic factor indirectness – in the subgroup with no contractile reserve it was not possible to determine whether it was true-severe AS or pseudo-severe AS based on increase/no increase in valve area and the study reports them as a separate, third group. However, for the multivariate analysis the no contractile reserve subgroup is combined with true-severe AS and it is unclear whether this group experienced an increase in valve area or not. Based on study characteristics table, only small increases in valve area reported in the no contractile reserve group so may all have shown no increase as well as in the true-severe AS group, though this is unclear.

(i) Methods: multivariable analysis, though confounders included in the reported multivariate analysis are unclear. May have included the following: aortic valve area at peak stress, absence of aortic valve area increase during stress, absence of contractile reserve and presence of significant coronary artery disease. If these were the included confounders, only one of those specified in the protocol has been included.

(j) Population indirectness – not limited to symptomatic low-flow AS as appears to include some that are asymptomatic (NYHA class I) – 87% are symptomatic low-flow AS. Outcome indirectness – combines medically and surgically treated patients in the same analysis and has not included this as a confounding factor, whereas in the protocol ideally separate results for those medically and surgically treated could be extracted

Table 10Table 9, Table 12, Table 13, Table 11, Table 14, Table 15.

Economic

- No relevant economic evaluations were identified.

1.1.12 The committee's discussion and interpretation of the evidence

1.1.121.1.12.1. The outcomes that matter most

All outcomes listed in the protocol were deemed critical and where possible they were assessed separately for groups that did not receive intervention (i.e. medically managed) and those that received an intervention (i.e. transcatheter or surgical intervention).

The following outcomes were pre-specified for each of these two treatment strategies:

- <u>Outcomes following no intervention (medical/conservative treatment):</u>
  - Mortality
  - Hospital attendance/admission for heart failure or unplanned intervention
  - Reduced cardiac function (echo or CMR parameters – for example LVEF <50% for AS and AR or LVEF <60% for MR)
  - Symptom onset (for those that were asymptomatic at enrolment in the study)

  Time-points selected for reporting of these outcomes were 1 and 5 years, where possible.

- <u>Outcomes following intervention (transcatheter or surgical treatment):</u>
  - Mortality
  - Hospital attendance for heart failure
  - Cardiac event-free survival

- Reduced cardiac function (echo or CMR parameters – for example LVEF <50%)

Time-points selected for reporting of these outcomes were 6 and 12 months, where possible.

The included evidence covered various types and presentations of valve disease, which were analysed as separate populations from the outset of the review. The evidence also covers a wide range of different risk factors pre-specified in the protocol. The number of outcomes reported therefore differs according to the type and presentation of valve disease and also the risk factor. However, in general, most reported outcomes were a composite of two or more different outcomes listed in the protocol.

Overall, most of the evidence was from populations that had been medically managed and censored at the time of surgery or need for surgery forming part of the outcome, though there were a number of studies that included medically and surgically treated patients in the same analysis and one study that looked solely at those that had received an intervention.

1.1.12.2 The quality of the evidence

Strata and risk factors covered

No evidence was identified for the following population strata: asymptomatic severe AR, asymptomatic severe MS and symptomatic non-severe MS.

Some evidence was identified for all other strata specified in the protocol, though the number of risk factors covered for each varied. The number of risk factors covered by at least one study and outcome for each stratum was as follows (note that for many, some indirectness relative to the protocol was observed):

- Asymptomatic severe AS: 5/12 pre-specified risk factors
- Symptomatic non-severe or low-flow AS: 2/4 pre-specified risk factors
- Asymptomatic severe MR: 3/8 pre-specified risk factors
- Symptomatic non-severe MR: 1/3 pre-specified risk factors

Note that some additional risk factors were partially covered as there were some included studies that used ‘positive exercise test’ or ‘positive stress echocardiogram’ as risk factors. Definitions of positive tests in these studies incorporated more than one of the risk factors listed in the protocol and therefore does not provide evidence individually

Quality and limitations

The quality of the evidence ranged from low to very low, with the majority being very low. The main reason for downgrading in all studies was risk of bias, though indirectness relative to the protocol was also an issue for many studies. Within the risk of bias rating, the most common reasons for downgrading were: limited reporting of patient characteristics, particularly those pre-specified as confounders in the protocol; a lack of or no mention of blinding to risk factor group when outcomes were assessed, which was the case in most studies and was an issue because most studies reported subjective or partially subjective outcomes (for example, decision to perform aortic valve replacement may be partially due to knowledge of that risk factor); confounding adjustment – though all studies had to have performed some multivariate analysis to be included, in most cases none of the four pre-specified confounders in the protocol were included in this analysis, though in some studies some of these pre-specified confounders were exclusion criteria for the study (for example, coronary artery disease and pulmonary disease were excluded from a number of studies); and in some studies, there were fewer than 10 events per covariate in the analysis, making the estimates less reliable.

For many of the studies, indirectness relative to the protocol was also a reason for downgrading. One reason for downgrading due to indirectness was population indirectness. For example, some studies reported on moderate or severe or mild-severe asymptomatic AS, rather than all participants having severe asymptomatic AS, as specified as one of the strata in the protocol. Similar population indirectness was also observed for many studies in the other strata.

Another common reason for indirectness was the definition of the risk factor that had been used. The two main reasons for risk factor indirectness were the following: studies combined more than one factor listed in the protocol as the risk factor, rather than reporting data separately for each of the different factors; and differences between the format of the risk factor reported in the study compared to as specified in the protocol, for example using a different threshold to that specified (e.g. one study used a threshold >1 mm for ST segment depression, while in the protocol a threshold of >2 mm was specified).

In a few studies, outcome indirectness was considered to be present. This was because they had included medically and surgically treated patients in the analysis and had not adjusted for this or censored at the time of surgery, meaning separate outcomes were not available for those that did not receive intervention and those that received intervention.

Although some studies reported similar risk factors in similar populations, no pooling was performed as there were differences between the studies, primarily in terms of the definitions used for the risk factor and the components of the composite outcome reported (e.g. aortic valve replacement or death reported in one study and symptoms in daily life or sudden death reported in another study).

Another limitation of the evidence is the size of the studies – all but one study included fewer than 200 participants, meaning results are based on small populations. Imprecision was not observed for many outcomes as confidence intervals did not cross the null line in many cases, which also means they were considered to be statistically significant predictors. However, for some outcomes confidence intervals were wide despite being considered a significant predictor of outcome, coming close to the null line in some cases, meaning there is uncertainty in the size of the effect.

It is important to note that although this review aims to assess which risk factors measured on stress testing or echocardiography indicate that intervention should be performed in various valve disease presentations, this is based on interpretation of outcomes with and without intervention. For example, if a particular risk factor appears to be associated with a worse outcome (e.g. higher mortality) on medical treatment compared to those without the risk factor, this may mean that intervention should be considered for those with this risk factor. However, unless sufficient separate information is available for the same risk factor in populations that received medical treatment and populations that received surgical treatment, it is difficult to be sure that surgery would improve the prognosis of those with the risk factor, as the risk factor could worsen the prognosis of all patients, regardless of whether medical treatment or intervention is selected. To make strong conclusions about whether intervention would improve the prognosis of people with particular risk factors, evidence comparing medical treatment and intervention within these subgroups in the form of an intervention review would be required, which is not addressed by this review. However, the committee agreed that groups that experience poor outcomes following surgery are likely to experience even poorer outcomes if only medical management is provided, as these prognostic groups are associated with poorer outcome compared to those without the prognostic factor, regardless of which treatment is performed, though it was agreed that surgery would be a better option in these patients if suitable. Evidence of a prognostic factor being associated with a negative outcome following medical or surgical treatment was therefore used to support it as an indicator for intervention, as the committee agreed that surgery would improve outcomes compared to medical management for patients within these groups associated with poorer prognosis.

Based on a combination of the limitations reported above, all recommendations for intervention were consider recommendations as there was insufficient evidence to support making offer recommendations. In addition, for some prognostic factors, though there was some evidence suggesting a role as a prognostic factor for worse outcome, the evidence was considered to be insufficient to make even a consider recommendation. The reasons the evidence was considered insufficient is described in detail in the benefits and harms section below for each specific factor.

1.1.12.3 Benefits and harms

Asymptomatic severe AS

Symptoms unmasked on exercise

There was evidence from three studies that symptoms unmasked on exercise is a significant predictor of poor outcome in those with asymptomatic severe AS that were medically managed. The outcomes reported varied between the studies (cardiovascular death, typical AS symptoms indicating aortic valve replacement or major adverse cardiac events in one study, development of spontaneous exertional symptoms or cardiovascular death in one study and cardiovascular death or aortic valve replacement in one study). The definition of symptoms on exercise also varied slightly between the studies (stopping prematurely due to limiting breathlessness or dizziness at <80% of their predicted workload or chest pain at any stage in one study, limiting breathlessness/chest discomfort or dizziness in one study and angor, syncope, pre-syncope or dyspnoea in one study). Although two of the three studies had issues with population indirectness as they included a proportion with moderate or moderate and mild asymptomatic AS, the evidence was still deemed sufficient to list symptoms unmasked on exercise as an indication for intervention in the asymptomatic severe AS population, as the point estimates and confidence intervals for all three studies were consistent with this being a risk factor for worse outcome. It was agreed that symptoms unmasked on exercise is a factor that is commonly used in current practice as an indication for intervention, so would not lead to a change in current practice. The committee noted that in asymptomatic severe AS, some patients may not report any symptoms at rest as they have adapted to the development of symptoms, for example by reducing their activity as they experience breathlessness on more strenuous activity. Exercise may reveal symptoms that were being masked at rest and is therefore an indication for intervention as it suggests symptomatic severe AS is actually present.

Mean gradient increase >20 mmHg during exercise

Although there was evidence from a single study that a mean gradient increase >20 mmHg measured on exercise compared to rest was a significant predictor of worse outcome in asymptomatic or minimally symptomatic patients with moderate or severe AS that were managed medically, the committee agreed that the evidence was not strong enough to be able to include this as a factor that should lead to intervention being considered in asymptomatic severe AS. Despite the results for the composite outcome of cardiovascular death or need for aortic valve replacement due to symptoms or left ventricular dysfunction suggesting a large increase of events in those with this increase in gradient, with no imprecision identified, it was agreed that this is not an observation that would usually lead to intervention being considered in asymptomatic severe AS and would therefore represent a change in practice, possibly leading to an increased number of stress echocardiography tests being requested. The included evidence was not considered to be strong enough to support such as change in practice, as the evidence for this factor was from a single study with population indirectness, as it included moderate as well as severe cases and some that were minimally symptomatic rather than asymptomatic. A research recommendation was not made as it was not an observation that is used in practice to make treatment decisions and it was therefore not an area that was prioritised for research recommendations. The committee

were confident that the recommendations that were made would identify the majority of people with an indication for intervention.

Absolute difference of BNP levels from rest to exercise (per 100 pg/ml increase from rest)

One study investigated the effect of increased BNP levels from rest to exercise, as a continuous variable using increments of 100 pg/ml, in a population with asymptomatic severe AS that were initially medically managed. The composite outcome reported was death or aortic valve replacement indicated by development of symptoms or left ventricular dysfunction. Although the point estimate and confidence intervals were consistent with this factor being a significant risk factor for worse outcome, it was agreed that it was difficult to incorporate this in a recommendation as it is unclear at which threshold this factor is likely to become prognostic and there is no included evidence that compares outcomes between those with an increase vs. no increase in BNP from rest to exercise. This was not prioritised by the committee for a research recommendation due to the practicalities of measuring BNP during exercise.

Abnormal blood pressure response to exercise

Three studies investigated whether an abnormal blood pressure response to exercise was associated with outcome in asymptomatic severe, asymptomatic moderate or severe, or asymptomatic mild-severe AS that received medical management. There was population indirectness for two of the three included studies as populations included moderate or moderate and mild cases as well as severe.

The definition of the risk factor varied slightly across all three studies and were as follows: sustained reduction of systolic blood pressure ≥20 mmHg below previous stage or baseline level; reduction or no increase in blood pressure compared to rest; and drop in systolic blood pressure ≥10 mmHg compared to rest.

There was some evidence from two studies to suggest that an abnormal blood pressure response to exercise is a significant risk factor for worse outcome in asymptomatic severe or asymptomatic moderate or severe AS (symptoms developing spontaneously during follow-up reported by one study, aortic valve replacement reported by one study and cardiovascular death or aortic valve replacement reported by one study). However, this was based only on the point estimate, as the confidence intervals demonstrated considerable uncertainty in the result, with all three outcomes reported across these two studies coming close to or crossing the line of no effect.

In addition, further uncertainty was added for this prognostic factor as the results for the third study suggest that an abnormal blood pressure response to exercise is not a risk factor for increased development of spontaneous exertional symptoms or cardiovascular death in asymptomatic mild-severe AS, where 8% of the population had mild AS. The confidence intervals for this outcome were quite narrow and consistent with it not being a risk factor for worse outcome.

Based on the uncertainty observed for this prognostic factor, it was agreed that there was insufficient evidence included to include abnormal blood pressure response to exercise as one of the factors that should lead to intervention being considered in asymptomatic severe AS. The committee did not prioritise this as an area for a research recommendation as they were confident that the recommendations made would identify the majority of people with an indication for intervention.

ST segment depression on exercise

Two studies investigated whether ST segment depression on exercise was associated with outcome in asymptomatic moderate or severe, or asymptomatic mild-severe AS that received medical management. There was population indirectness for both of the included studies as populations included moderate or moderate and mild cases as well as severe.

The definition of the risk factor varied slightly between the two studies as one used a threshold of ≥2 mm for ST segment depression and the other used a threshold of >1 mm for downsloping ST segment depression.

Based on the point estimates, different results were observed in the two studies. One suggested downsloping ST segment depression (>1 mm) was a significant risk factor for cardiovascular death or aortic valve replacement. However, there is uncertainty in this estimate as the confidence intervals are fairly wide and come close to the line of no effect. The other suggested that ST depression (≥2 mm) was not a significant risk factor for the development of spontaneous exertional symptoms or cardiovascular death, with confidence intervals being very narrow and just crossing the null line.

Overall, there was not considered to be sufficient evidence to include this factor as one of the factors that should lead to intervention being considered in asymptomatic severe AS. The committee did not prioritise this as an area for a research recommendation as they were confident that the recommendations made would identify the majority of people with an indication for intervention.

Positive or abnormal exercise test – various definitions included

Three studies investigated whether the risk factor of a positive or abnormal exercise test was associated with outcome in a population with asymptomatic severe (one study) or asymptomatic moderate or severe (two studies) AS under medical treatment. The definition of a positive or abnormal exercise test incorporated multiple risk factors listed in the protocol and differed slightly between the three studies. Though differing slightly between the studies, the definitions included most of the following on exercise in each study: ST segment depression; symptoms, such as angina, dizziness, presyncope and syncope; complex ventricular arrythmia, a rise in or failure of blood pressure to rise ≥20 mmHg.

Mixed results were observed, as one study suggested that the group with a positive exercise test had higher events in terms of appearance of symptoms in daily life or sudden death in asymptomatic severe AS, which was demonstrated to be significant as the confidence intervals did not cross the null line, while the other two studies suggested no or only a small effect in opposing directions for the development of significant symptoms, need for aortic valve replacement or cardiac-related death. It is important to note that there may be some overlap between the latter two studies as they have very similar inclusion criteria, though the definition of the prognostic factor differs slightly.

It was agreed that these studies are less useful than those that provided results for individual prognostic factors on exercise testing separately rather than combining multiple under 'abnormal exercise test', as it does not provide any further information as to which specific observations on exercise testing should lead to intervention being considered.

The committee did not prioritise this as an area for a research recommendation as they were confident that the recommendations made would identify the majority of people with an indication for intervention.

Symptomatic low-flow low-gradient AS

No increase in valve area on dobutamine stress testing

Evidence from two studies demonstrated that no increase in valve area on dobutamine stress testing was associated with worse outcome (overall mortality in one study and death, myocardial infarction or significant worsening of heart failure symptoms in one study) in symptomatic low-flow low-gradient AS, though in one study ~13% were asymptomatic rather than symptomatic, meaning the population was indirect. In one study, all patients were managed conservatively for >6 months but in the other the population was a mixture of those that received conservative management and those that received surgery, with no adjustment for surgery being performed in the analysis.

The definition of the risk factor and the comparator used varied slightly between the two studies. One used no increase in valve area to >1.2 cm^2 or no contractile reserve as the risk factor and compared it to those that did have an increase in valve area to >1.2 cm^2 on dobutamine testing, while the other used no increase in valve area as the risk factor and compared it to those that did have an increase in valve area on dobutamine testing. For those with low-flow low-gradient AS but where the valve area is <1.0 cm^2 and suggests severe AS at rest, a lack of an increase in valve area on dobutamine testing to within the moderate range suggests that the AS may actually be severe, despite low flow and low gradient at rest suggesting the AS is not severe.

Based on the fact that point estimates and confidence intervals from both studies were consistent with no increase in valve area on dobutamine testing being associated with worse outcome, as the confidence intervals did not cross the null line meaning this was a significant predictor of outcome, the committee agreed that there was sufficient evidence to include this as a factor that should lead to intervention being considered in those with symptomatic low-flow AS. It was agreed that in this population with symptoms, a lack of an increase in valve area to within the moderate range on dobutamine testing was currently used as an indication for intervention and would not represent a change in practice.

Increase of mean gradient to within severe range on dobutamine stress testing

One study investigated whether increase of mean gradient to within the severe range (≥ 40 mmHg) on dobutamine stress testing was associated with outcome in low-flow low-gradient AS, where at least 40% where symptomatic as they were reported to be in NYHA class III or IV. However, it was unclear whether the remaining 60% were symptomatic and the population was therefore indirect. All patients were medically managed for analysis.

Based on a single study where there was substantial uncertainty in the result based on the confidence intervals and point estimate for the outcome of mortality, it was agreed that there was insufficient evidence to include this factor as one of the factors that should lead to intervention being considered in symptomatic low-flow low-gradient AS as it was not demonstrated to be a significant predictor of outcome. This area was not prioritised for a research recommendation as the committee were able to make a recommendation covering this population as referral for intervention for those with no increase in valve area on dobutamine stress testing was recommended, while populations included in the research recommendations were those where no recommendations could currently be made.

Asymptomatic severe MR

Increase of SPAP to >60 mmHg on exercise testing

There was evidence from two studies that an increase of systolic pulmonary artery pressure SPAP to >60 mmHg on exercise (exercise pulmonary hypertension) was associated with worse outcome (development of symptoms, including shortness of breath, angina, dizziness or syncope with exertion, during follow-up in one study and cardiovascular death, cardiovascular hospitalisation, stroke or atrial fibrillation in one study) in asymptomatic or

asymptomatic/mildly symptomatic moderate or severe MR, with it demonstrated to be a significant predictor of outcome. Both studies included some that had moderate asymptomatic or mildly symptomatic MR rather than severe and the population was therefore indirect. One study reported the outcome in a medically managed population and the other covered only those that were surgically managed.

It was agreed that the outcomes reported in the two studies were limited, as one only reported on the development of symptoms, with no information for mortality or other serious outcomes, and for the other study atrial fibrillation events made up a large proportion of the observed events for the composite outcome, which is a weaker outcome compared to other events such as cardiovascular mortality and cardiovascular hospitalisation. However, although it was noted that evidence confirming improved outcomes if intervention if performed prior to rather than following the development of symptoms in severe MR is limited, the committee agreed that intervening prior to symptom development may be preferable and evidence from one study included in the review reported an association between SPAP >60 mmHg on exercise and the development of symptoms during follow-up.

Despite the confidence intervals of one of the studies coming close to the line of no effect, based on the fact that the point estimates from both studies were consistent with an increase of SPAP to >60 mmHg on exercise being associated with worse outcome, the committee agreed that, despite the limitations, there was sufficient evidence to include this as a factor that should lead to intervention being considered in those with asymptomatic severe MR. This decision was also partly based on the clinical experience of the committee, as it was noted that SPAP >60 mmHg may be associated with worse prognosis if intervention is not performed. It was also agreed that this observation on exercise testing is increasingly being used in this population as a possible indicator for intervention and would therefore be consistent with current practice. A recommendation was made for this indicator.

Lack of contractile reserve on stress testing

Two studies investigated whether a lack of contractile reserve on stress testing was associated with outcome in asymptomatic moderate or severe primary MR (one study using exercise testing) or asymptomatic/mildly symptomatic moderate-severe or severe functional MR (one study using dobutamine testing). Both studies included some that had moderate asymptomatic or mildly symptomatic MR rather than severe asymptomatic MR and the population was therefore indirect. One study reported the outcome in a medically managed population but in the other the population was a mixture of those that received conservative management and those that received surgery, with no adjustment for surgery being performed in the analysis.

Slightly different definitions were used to indicate a lack of contractile reserve. The study that covered medically managed primary MR patients defined a lack of contractile reserve as <2% improvement in global longitudinal strain on exercise testing, while the study covering medically and surgically managed functional MR patients defined it as <10% improvement in global left ventricular function on dobutamine testing.

For both studies, the point estimate indicates that a lack of contractile reserve is a significant risk factor for worse outcome within their respective populations. A <2% improvement in global longitudinal strain was a risk factor for cardiac events (cardiovascular death, indication for mitral valve surgery due to symptoms or left ventricular dysfunction, or hospitalisation for acute pulmonary oedema or congestive heart failure) in medically managed primary MR patients. For both adjusted estimates from this study, the lower confidence interval comes quite close to the line of no effect, suggesting there is uncertainty in whether this is a risk factor for worse outcome. In addition, <10% improvement in global left ventricular function was demonstrated to be a risk factor for all-cause mortality or need for heart transplant in medically or surgically managed functional MR patients.

Despite both studies suggesting increased events in those without contractile reserve on stress testing, it was agreed that the evidence included was not strong enough to be able to make recommendations for this factor as only a single study was identified for primary and secondary MR, respectively, and it was agreed they should be considered separately as they are very different types of MR. A single, small study with evidence that was graded very low quality for each was not considered to be enough for this factor as it is not currently used as an indicator for intervention in asymptomatic severe MR and would represent a change in practice. This area was not prioritised for a research recommendation as it is not an observation that is usually used when making treatment decisions and the committee were able to make a recommendation covering this population as referral for intervention for those with an increase of SPAP >60 mmHg was recommended, while populations included in the research recommendations were those where no recommendations could currently be made.

Exercise capacity (VO_2 max) ≤84% predicted for weight, age and gender

One study investigated whether an exercise capacity (measured by VO_2 max) ≤84% predicted for weight, age and gender was associated with outcome in those with asymptomatic moderate or severe organic MR that were medically managed, with the population being indirect due to the inclusion of some with asymptomatic moderate organic MR. The threshold used for the prognostic factor was also a source of indirectness, as <60% had been pre-specified in the protocol.

Although the point estimate suggested that this was a risk factor for clinical events (death, heart failure or new severe symptoms, or new atrial arrythmia) and it was considered to be a significant risk factor as the null line was not crossed, uncertainty was present as the lower confidence interval comes close to the line of no effect. It was therefore agreed that based on the uncertainty in the result and the fact only a single, small study was included for this factor with evidence graded very low quality, there was insufficient evidence to include this as a factor that should lead to intervention being considered in those with asymptomatic severe primary MR.

This area was not prioritised for a research recommendation as the committee were able to make a recommendation covering this population as referral for intervention for those with an increase of SPAP >60 mmHg was recommended, while populations included in the research recommendations were those where no recommendations could currently be made.

Symptomatic non-severe MR

Severe status unmasked on exercise

One study investigated whether an increase in effective regurgitant orifice area by ≥13 mm^2 was associated with two different outcomes in symptomatic non-severe functional MR, though there was population indirectness as 32% of the included participants had severe symptomatic MR rather than non-severe symptomatic MR. There was also indirectness regarding the prognostic factor, as it was not clear whether an increase of ≥13 mm^2 would represent the unmasking of severe disease on exercise in all participants, particularly for those with very mild MR at rest. All patients were medically managed for the analysis and censored from the analysis if surgery was performed.

The results indicated that an increase in effective regurgitant orifice area by ≥13 mm^2 is a significant risk factor for cardiac death and hospital admission for heart failure in this study, which consisted of those with functional MR. However, due to the limitations of the study in terms of population indirectness and it being unclear whether an increase of ≥13 mm^2 for regurgitant orifice area represents the unmasking of severe disease in all cases, the committee agreed that the evidence was not strong enough to include this as a factor that

should lead to intervention being considered in those with symptomatic non-severe functional MR. Therefore, no recommendations covering symptomatic non-severe MR were made but a research recommendation investigating the association between the unmasking of severe disease on exercise echocardiography and outcomes in symptomatic non-severe MR was made (see Appendix K.1.5 for details).

Any valve disease

Positive exercise echocardiogram

One study investigated whether a positive exercise echocardiogram, which had various definitions depending on the type and presentation of valve disease, was associated with outcome. The study did not focus on a specific type of valve disease (e.g. asymptomatic severe AS or symptomatic non-severe MR) and instead included various different types: asymptomatic severe AS, asymptomatic severe AR, asymptomatic severe MS, symptomatic non-severe MS, asymptomatic severe MR and symptomatic non-severe MR. In addition, the analysis includes those that were medically managed and those that were surgically managed, with no adjustment for this in the analysis.

The definition of a positive exercise echocardiogram differed depending on the valve disease, as follows: symptomatic non-severe MR, increase in severity to severe – effective orifice area ≥0.4 cm^2 (organic) or ≥0.2 cm^2 (functional); asymptomatic severe MR, increase in SPAP to >60 mmHg; symptomatic non-severe MS, increase in mean transmitral gradient ≥15 mmHg or estimated SPAP to ≥60 mmHg; asymptomatic severe MS, increase in mean transmitral gradient ≥15 mmHg or estimated SPAP to ≥60 mmHg or symptom development; asymptomatic severe AS, increase in mean transaortic gradient ≥20 mmHg; and asymptomatic severe AR, lack of increase in left ventricular ejection fraction ≥5% or exercise-induced reduction in left ventricular ejection fraction.

The results indicate that a positive exercise echocardiogram is a significant risk factor for admission for worsening heart failure or death in heart valve disease in general, based on the point estimate and confidence intervals.

Despite the results demonstrating a large increase in events in those with a positive exercise echocardiogram compared to those with a negative exercise echocardiogram, with a point estimate >15.0 and suggesting a positive exercise echocardiogram is a risk factor for worse outcome in valve disease overall, it was agreed that this result is difficult to interpret as multiple heart valve disease presentations and risk factors on exercise testing have been combined. For example, it might be that a positive exercise echocardiogram is a risk factor in some of the included populations but less of a risk factor in others, and it would therefore not be appropriate to use a positive exercise echocardiogram to suggest poorer prognosis in all types of valve disease. Similarly, for some of the included heart valve disease populations, multiple different observations on exercise testing have been used to indicate a positive echocardiogram, some of which may be more of a risk factor for poor outcome than others.

A research recommendation was not prioritised for this area due to the heterogeneity of the population which would make research difficult to conduct.

Asymptomatic severe AR

No evidence was included in the review to cover this population. Due to variation in current practice a consensus recommendation could not be made. This was considered to be an area where further research would be useful as there are questions about when to intervene in this population. Therefore, a research recommendation was made to identify prognostic factors in this population on stress testing (see Appendix K.1.1 for details).

Asymptomatic severe MS and symptomatic non-severe MS

No evidence was identified covering either of these populations for this review. Due to variation in current practice a consensus recommendation could not be made. Research recommendations in these populations were discussed, however, the committee agreed that this population of patients is very small and in their experience stress testing was not commonly performed in practice. For these reasons, this population was not considered to be a priority for further research on prognostic factors on stress testing.

1.1.12.4 Cost effectiveness and resource use

No health economic evidence was identified. The committee made separate recommendations for factor that should lead to intervention being considered in some populations where clinical evidence was found. These factors are Vmax more than 5 m/s, LVEF less than 60%, BNP level more than twice the upper limit of normal, symptoms unmasked on exercise, low gradient across the aortic valve, a valve area less than 1.0 cm2, ESDI more than 2.2 cm/m2 on echocardiography, an increase of systolic pulmonary artery pressure to more than 60 mgHg on exercise testing. The factors included in the recommendations are commonly used in current practice as an indication for intervention, so would not lead to a change in current practice.

In addition, the committee noted that the presence of these specific factors in the different populations means the patient could truly have an underlying condition that would need intervention and if not treated or investigated early can lead to downstream complications and increase in NHS costs.

The committee did not make recommendations where there was insufficient clinical evidence and uncertainty in clinical practice as some factors could lead to a possible increase in intervention being considered and tests being requested and therefore likely to have additional costs to the NHS.

1.1.13 Recommendations supported by this evidence review

This evidence review supports recommendations 1.3.2, 1.3.3 and 1.3.8 and the research recommendation on stress testing and stress echocardiography to determine the need for intervention.

1.1.14 References

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Appendices

Appendix A – Review protocols

Review protocol for stress testing and stress echocardiography in determining need for intervention

ID	Field	Content
0.	PROSPERO registration number	CRD42020181671
1.	Review title	In adults with heart valve disease, what is the prognostic value and cost effectiveness of stress testing and stress echocardiography to determine the need for intervention?
2.	Review question	In adults with heart valve disease, what is the prognostic value and cost effectiveness of stress testing and stress echocardiography to determine the need for intervention?
3.	Objective	To assess the prognostic value of stress testing and stress echocardiography to determine the need for intervention in adults with diagnosed heart valve disease.
4.	Searches	The following databases (from inception) will be searched: • Embase • MEDLINE Searches will be restricted by: • English language • Human studies • Letters and comments are excluded

		Other searches: • Inclusion lists of relevant systematic reviews will be checked by the reviewer. The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review.
5.	Condition or domain being studied	Diagnosed heart valve disease in adults aged 18 years and over: Aortic (including bicuspid) stenosis, aortic regurgitation, mitral stenosis, mitral regurgitation and tricuspid regurgitation.
6.	Population	Inclusion: Adults aged 18 years and over with diagnosed heart valve disease requiring further tests after echocardiography to determine if intervention is needed. This may be because they are symptomatic but do not have severe HVD or are asymptomatic with severe HVD, stratified by the type of heart valve disease as well as symptomatic status as follows: • Asymptomatic severe aortic [including bicuspid] stenosis • Symptomatic non-severe aortic [including bicuspid] stenosis • Asymptomatic severe aortic regurgitation • Asymptomatic severe mitral stenosis • Symptomatic non-severe mitral stenosis • Asymptomatic severe mitral regurgitation • Symptomatic non-severe mitral regurgitation Inclusion of indirect evidence: Studies including mixed populations will be included (and downgraded for indirectness) if >75% of the included patients meet the protocol criteria.

		If limited evidence is available, studies with a mixed severe/non-severe population (including mixed moderate/severe) or mixed symptomatic status will be considered for inclusion with downgrading for indirectness Exclusion: Children (aged less than 18 years). Adults with congenital heart disease (excluding bicuspid aortic valves). Tricuspid stenosis and pulmonary valve disease. Adults with previous intervention for HVD (surgical or transcatheter) For asymptomatic heart valve disease, secondary heart valve disease because it does not occur in the asymptomatic group Adults with acute heart failure Note: Populations with multiple valve disease will not be excluded from the protocol. For populations with multiple valve disease, studies will be classified into strata based on the heart valve disease that drives the need for intervention (e.g. most severe valve disease).
7.	Predictors/prognostic factors for intervention	The following parameters will be assessed according to the type of HVD. Functional and anatomical parameters refer to measurements from pharmacological stress or exercise echocardiography: <u>1. Mitral regurgitation</u> **Asymptomatic severe MR** Exercise stress testing: • Exercise capacity <60% predicted workload for gender, age and weight

		• Symptoms unmasked in response to exercise • Increase in BNP levels on exercise compared with baseline • Development of significant arrhythmia on exercise Exercise stress echocardiography: • Decrease in LVEF on exercise compared with baseline • Reduced left ventricular systolic function based on global longitudinal strain on exercise compared with baseline • Increase in peak systolic pulmonary artery pressure during low workload exercise to >60 mmHg (SPAP >60 mmHg) • Lack of demonstrated contractile reserve at low workload exercise **Symptomatic non-severe MR** Exercise or pharmacological stress testing: • Exercise capacity <60% predicted workload for gender, age and weight • Increase in BNP levels on exercise compared with baseline • Exercise echocardiography: Severe status unmasked in response to pharmacological stress or exercise <u>2. Aortic stenosis</u> **Asymptomatic severe AS** Exercise stress testing: • Exercise capacity <60% predicted workload for gender, age and weight • Symptoms unmasked in response to exercise • Increase in BNP levels on exercise compared with baseline

		• Reduction of blood pressure by >20 mmHg or no rise in blood pressure during exercise • ST depression on ECG by >2 mm during exercise in the absence of coronary disease • Development of significant arrhythmia on exercise Exercise stress echocardiography: • Decrease in LVEF on pharmacological stress or exercise compared with baseline • Reduced left ventricular systolic function based on global longitudinal strain on pharmacological stress or exercise compared with baseline • Worsening in parameters of diastolic function / indicators of left atrial filling pressure (E/e') on exercise compared with baseline – E/e' >15 on exercise • Mean gradient increase >20mmHg during exercise • Induced ischaemia (regional wall motion abnormalities) during exercise in the absence of coronary disease • Development of moderate or severe mitral regurgitation on exercise **Symptomatic non-severe or low-flow AS** Exercise stress testing: • Exercise capacity <60% predicted workload for gender, age and weight Pharmacological or exercise stress echocardiography:

		• Severe status unmasked in response to pharmacological stress or exercise, e.g., Increase in peak and mean gradient on pharmacological stress or exercise to within the severe range • No increase in aortic valve area on pharmacological stress or exercise • Mean gradient increase >20mmHg during pharmacological stress or exercise 3. Aortic regurgitation **Asymptomatic severe AR** Exercise stress testing: • Exercise capacity <60% predicted workload for gender, age and weight • Symptoms unmasked in response to exercise • Increase in BNP levels on exercise compared with baseline Exercise stress echocardiography: • Lack of demonstrated contractile reserve at low workload exercise • Decrease in LVEF on exercise compared with baseline • Reduced left ventricular systolic function based on global longitudinal strain on exercise compared with baseline 4. Mitral stenosis **Asymptomatic severe MS** Exercise stress testing: • Exercise capacity <60% predicted workload for gender, age and weight • Symptoms unmasked in response to exercise

		Symptomatic non-severe MS Exercise stress testing: • Exercise capacity <60% predicted workload for gender, age and weight Pharmacological or exercise stress echocardiography: • Severe status unmasked in response to pharmacological stress or exercise, eg Increase in mitral valve mean gradient on stress/exercise to severe range – pharmacological stress and exercise • Increase in peak systolic pulmonary artery pressure during low workload exercise to >60 mmHg (SPAP >60 mmHg) – only during exercise
8.	Confounding factors	• Coronary disease • Comorbid lung disease or respiratory insufficiency • Peripheral vascular disease • Arthritis
9.	Types of study to be included	• Prospective and retrospective cohort studies that control for confounders in the study design or analysis • Systematic reviews of the above • If no cohort studies are identified case control studies that control for confounders in the study design or analysis will be included but downgraded for risk of bias. This will be assessed separately for each test and population.
10.	Other exclusion criteria	Exclusion criteria: • Conference abstracts will be excluded because they are unlikely to contain enough information to assess whether the population matches the review question in terms of previous medication use, or enough detail on outcome definitions, or on the methodology to assess the risk of bias of the study. • Studies that have not accounted for confounders in the design or analysis

		• Non-English language studies • Studies where the reason for intervention is a separate cardiac problem (e.g. coronary artery disease) and the heart valve is operated on at the same time
11.	Context	Among adults with diagnosed heart valve disease who have had an initial echocardiography assessment, some require further tests to determine if intervention is needed because there is a mismatch between symptoms and severity. This may be because they are symptomatic but do not have severe HVD or are asymptomatic with severe HVD. Stress testing and stress echo are common techniques used in this population to provide additional information on the severity of the disease and/or to unmask symptoms that may not have been apparent.
12.	Primary outcomes (critical outcomes)	Indication for intervention based on prognosis for the following without intervention: • Mortality (1 and 5 years) • Hospital attendance/admission for heart failure or unplanned intervention (1 and 5 years) • Reduced cardiac function (echo or CMR parameters – for example LVEF <50% for AS and AR or LVEF <60% for MR) (1 and 5 years) • Symptom onset (for those that were asymptomatic at enrolment in the study) (1 and 5 years) Indication for intervention based on predictors of the following post-operative outcomes and time-points: • Mortality (6 and 12 months) • Hospital attendance for heart failure (6 and 12 months) • Cardiac event-free survival • Reduced cardiac function (echo or CMR parameters – for example LVEF <50%) (6 and 12 months) This may be reported as an adjusted HR, RR or OR.

		Sensitivity, specificity and AUC will not be included as these do not allow for multivariable adjustment. Use the time point closest to each of the listed endpoints and combine data as follows: 6 months: include 0-6 months 12 months: include >6 months up to 12 months 1 year: include 0-12 months 5 years: include all >1 year. No minimum follow-up.
13.	Secondary outcomes (important outcomes)	N/A
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). This will include study design, analysis method, population source, baseline population characteristics, confounding factors accounted for, numbers in each prognostic group, numbers of events, and calculated effect estimate when reported.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. • The QUIPS checklist will be used to assess risk of bias of each individual study. 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking:

		• papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
16.	Strategy for data synthesis	• Pooling will be considered if the population, prognostic factor, outcomes, confounders and analysis are sufficiently similar. It is not necessary for the exact same confounders to be adjusted for because only the key confounders, with higher coefficients of determination, will noticeably affect the effect size. Many of the other confounders will have a relatively small effect on the point estimate so it may be appropriate to pool studies with slightly different arrays of confounding variables. This is judged on a case-by-case basis. • Where data allows, pairwise meta-analysis will be performed using Cochrane Review manager (RevMan5) software. A fixed-effect meta-analysis, with hazard ratios, odds ratios or risk ratios (as appropriate), and 95% confidence intervals will be calculated for each outcome. • Data from the meta-analysis will be presented and quality assessed in adapted GRADE tables taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each risk factor. Publication or other bias will only be taken into consideration in the quality assessment if it is apparent. • Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic. We will consider an I^2 value greater than 50% indicative of substantial heterogeneity. We will conduct sensitivity analyses based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented using random-effects.

		• If meta-analysis is not possible or appropriate, results will be reported individually per outcome in adapted GRADE tables. A second reviewer will quality assure 10% of the data analyses. Discrepancies will be identified and resolved through discussion (with a third party where necessary).	
17.	Analysis of sub-groups	**Groups that will be analysed separately (strata):** **Population:** Stratified by the type of heart valve disease as well as symptomatic status as follows: • Asymptomatic severe aortic [including bicuspid] stenosis • Symptomatic non-severe aortic [including bicuspid] stenosis • Asymptomatic severe aortic regurgitation • Asymptomatic severe mitral stenosis • Symptomatic non-severe mitral stenosis • Asymptomatic severe mitral regurgitation • Symptomatic non-severe mitral regurgitation **Subgroups that will be investigated if heterogeneity is present:** None identified	
18.	Type and method of review	☐	Intervention
		☐	Diagnostic
		☒	Prognostic
		☐	Qualitative

		☐	Epidemiologic
		☐	Service Delivery
		☐	Other (please specify)
19.	Language	English	
20.	Country	England	
21.	Anticipated or actual start date	09/05/2019	
22.	Anticipated completion date	17/06/2021	
23.	Stage of review at time of this submission	Review stage	Started / Completed
		Preliminary searches	☑ / ☑
		Piloting of the study selection process	☑ / ☑
		Formal screening of search results against eligibility criteria	☑ / ☑
		Data extraction	☑ / ☑
		Risk of bias (quality) assessment	☑ / ☑
		Data analysis	☑ / ☑
24.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail HVD@nice.org.uk	

		5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre
25.	Review team members	From the National Guideline Centre: Sharon Swain [Guideline lead] Eleanor Samarasekera [Senior systematic reviewer] Nicole Downes [Systematic reviewer] George Wood [Systematic reviewer] Robert King [Health economist] Jill Cobb [Information specialist] Katie Broomfield [Project manager]
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.

28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10122	
29.	Other registration details	None	
30.	Reference/URL for published protocol		
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	Aortic regurgitation; aortic stenosis; echocardiography; heart valve disease; mitral regurgitation; mitral stenosis; prognosis; stress testing; stress echocardiography; tricuspid regurgitation	
33.	Details of existing review of same topic by same authors	N/A	
34.	Current review status	☐	Ongoing
		☒	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued

35.	Additional information	N/A
36.	Details of final publication	www.nice.org.uk

1

Table 16: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2004, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[178] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).

	• OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2004 or later that depend on unit costs and resource data entirely or predominantly from before 2004 will be rated as 'Not applicable'. • Studies published before 2004 will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B Literature search strategies

Heart valve disease – search strategy 3 - stress testing and echocardiography

This literature search strategy was used for the following review:

- In adults with heart valve disease, what is the prognostic value and cost effectiveness of stress testing and stress echocardiography to determine the need for intervention?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[178]

For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 17: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 14 October 2020	Exclusions
Embase (OVID)	1974 – 14 October 2020	Exclusions

Medline (Ovid) search terms

1.	exp Heart Valve Diseases/
2.	exp heart valves/
3.	((primary or secondary) adj valv* disease*).ti,ab.
4.	((valv* or flap* or leaflet*) adj1 (heart or cardiac) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)).ti,ab.
5.	((mitral or aortic or tricuspid or pulmon*) adj (valv* or flap* or leaflet*) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)).ti,ab.
6.	((mitral or aortic or tricuspid or pulmon*) adj3 (prolapse or regurgitation or stenos?s or atresia or insufficienc*)).ti,ab.
7.	exp Heart Murmurs/
8.	((heart or cardiac) adj murmur*).ti,ab.
9.	or/1-8
10.	letter/
11.	editorial/
12.	news/
13.	exp historical article/
14.	Anecdotes as Topic/
15.	comment/
16.	case report/
17.	(letter or comment*).ti.
18.	or/10-17
19.	randomized controlled trial/ or random*.ti,ab.
20.	18 not 19
21.	animals/ not humans/
22.	exp Animals, Laboratory/
23.	exp Animal Experimentation/
24.	exp Models, Animal/
25.	exp Rodentia/
26.	(rat or rats or mouse or mice).ti.
27.	or/21-26
28.	9 not 27
29.	limit 28 to English language

30.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
31.	29 not 30
32.	Predictive Value of Tests/
33.	Echocardiography, Stress/
34.	Dobutamine/ or dobutamine.ti,ab.
35.	(stress adj2 (pharma* or drug* or chemical)).ti,ab.
36.	(stress adj (cardiac or heart or cardiograph* or echo* or ECG or ultrasonic or ultrasound)).ti,ab.
37.	exp Exercise Test/
38.	((physical* or exercise* or fitness) adj4 (endur* or exert* or capacit* or tolera* or test* or stress*)).ti,ab.
39.	or/32-38
40.	31 and 39

1 **Embase (Ovid) search terms**

1.	exp valvular heart disease/
2.	exp heart valve/
3.	((primary or secondary) adj valv* disease*).ti,ab.
4.	((valv* or flap* or leaflet*) adj1 (heart or cardiac) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)).ti,ab.
5.	((mitral or aortic or tricuspid or pulmon*) adj (valv* or flap* or leaflet*) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)).ti,ab.
6.	((mitral or aortic or tricuspid or pulmon*) adj3 (prolapse or regurgitation or stenos?s or atresia or insufficienc*)).ti,ab.
7.	exp heart murmur/
8.	((heart or cardiac) adj murmur*).ti,ab.
9.	or/1-8
10.	letter.pt. or letter/
11.	note.pt.
12.	editorial.pt.
13.	Case report/ or Case study/
14.	(letter or comment*).ti.
15.	or/10-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animal/ not human/
19.	Nonhuman/
20.	exp Animal Experiment/
21.	exp Experimental animal/
22.	Animal model/
23.	exp Rodent/
24.	(rat or rats or mouse or mice).ti.
25.	or/18-24
26.	9 not 25
27.	limit 26 to English language

28.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
29.	27 not 28
30.	predictive value/
31.	Echocardiography, Stress/
32.	Dobutamine/ or dobutamine.ti,ab.
33.	(stress adj2 (pharma* or drug* or chemical)).ti,ab.
34.	(stress adj (cardiac or heart or cardiograph* or echo* or ECG or ultrasonic or ultrasound)).ti,ab.
35.	exercise test/
36.	((physical* or exercise* or fitness) adj4 (endur* or exert* or capacit* or tolera* or test* or stress*)).ti,ab.
37.	or/30-36
38.	29 and 37

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to heart valve disease population in NHS Economic Evaluation Database (NHS EED) – (this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) – (this ceased to be updated after March 2018) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics.

Table 18: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	01 January 2014 – 15 October 2020	Exclusions Health economics studies
Embase	01 January 2014 – 15 October 2020	Exclusions Health economics studies
Centre for Research and Dissemination (CRD)	HTA - Inception – 31 March 2018 NHSEED - Inception to 31 March 2015	None

Medline (Ovid) search terms

1.	exp Heart Valve Diseases/
2.	exp heart valves/
3.	((primary or secondary) adj valv* disease*).ti,ab.
4.	((valv* or flap* or leaflet*) adj1 (heart or cardiac) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)).ti,ab.
5.	((mitral or aortic or tricuspid or pulmon*) adj (valv* or flap* or leaflet*) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)).ti,ab.
6.	((mitral or aortic or tricuspid or pulmon*) adj3 (prolapse or regurgitation or stenos?s or atresia or insufficienc*)).ti,ab.
7.	Heart Valve Prosthesis/
8.	((mechanical or artificial or prosthe* or bioprosthe* or biological or tissue) adj (valv* or flap* or leaflet*)).ti,ab.
9.	valve-in-valve.ti,ab.

10.	(transcatheter adj2 (valve or valves)).ti,ab.
11.	exp Heart Murmurs/
12.	((heart or cardiac) adj murmur*).ti,ab.
13.	or/1-12
14.	letter/
15.	editorial/
16.	news/
17.	exp historical article/
18.	Anecdotes as Topic/
19.	comment/
20.	case report/
21.	(letter or comment*).ti.
22.	or/14-21
23.	randomized controlled trial/ or random*.ti,ab.
24.	22 not 23
25.	animals/ not humans/
26.	exp Animals, Laboratory/
27.	exp Animal Experimentation/
28.	exp Models, Animal/
29.	exp Rodentia/
30.	(rat or rats or mouse or mice).ti.
31.	or/24-30
32.	13 not 31
33.	limit 32 to english language
34.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
35.	33 not 34
36.	Economics/
37.	Value of life/
38.	exp "Costs and Cost Analysis"/
39.	exp Economics, Hospital/
40.	exp Economics, Medical/
41.	Economics, Nursing/
42.	Economics, Pharmaceutical/
43.	exp "Fees and Charges"/
44.	exp Budgets/
45.	budget*.ti,ab.
46.	cost*.ti.
47.	(economic* or pharmaco?economic*).ti.
48.	(price* or pricing*).ti,ab.
49.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.

50.	(financ* or fee or fees).ti,ab.
51.	(value adj2 (money or monetary)).ti,ab.
52.	or/36-51
53.	35 and 52

1 **Embase (Ovid) search terms**

1.	exp valvular heart disease/
2.	exp heart valve/
3.	((primary or secondary) adj valv* disease*).ti,ab.
4.	((valv* or flap* or leaflet*) adj1 (heart or cardiac) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)).ti,ab.
5.	((mitral or aortic or tricuspid or pulmon*) adj (valv* or flap* or leaflet*) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)).ti,ab.
6.	((mitral or aortic or tricuspid or pulmon*) adj3 (prolapse or regurgitation or stenos?s or atresia or insufficienc*)).ti,ab.
7.	exp heart valve prosthesis/
8.	((mechanical or artificial or prosthe* or bioprosthe* or biological or tissue) adj (valv* or flap* or leaflet*)).ti,ab.
9.	valve-in-valve.ti,ab.
10.	(transcatheter adj2 (valve or valves)).ti,ab.
11.	exp heart murmur/
12.	((heart or cardiac) adj murmur*).ti,ab.
13.	or/1-12
14.	letter.pt. or letter/
15.	note.pt.
16.	editorial.pt.
17.	Case report/ or Case study/
18.	(letter or comment*).ti.
19.	or/14-18
20.	randomized controlled trial/ or random*.ti,ab.
21.	19 not 20
22.	animal/ not human/
23.	Nonhuman/
24.	exp Animal Experiment/
25.	exp Experimental animal/
26.	Animal model/
27.	exp Rodent/
28.	(rat or rats or mouse or mice).ti.
29.	or/21-28
30.	13 not 29
31.	limit 30 to English language
32.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
33.	31 not 32
34.	health economics/

35.	exp economic evaluation/
36.	exp health care cost/
37.	exp fee/
38.	budget/
39.	funding/
40.	budget*.ti,ab.
41.	cost*.ti.
42.	(economic* or pharmaco?economic*).ti.
43.	(price* or pricing*).ti,ab.
44.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
45.	(financ* or fee or fees).ti,ab.
46.	(value adj2 (money or monetary)).ti,ab.
47.	or/34-46
48.	33 and 47

1 **NHS EED and HTA (CRD) search terms**

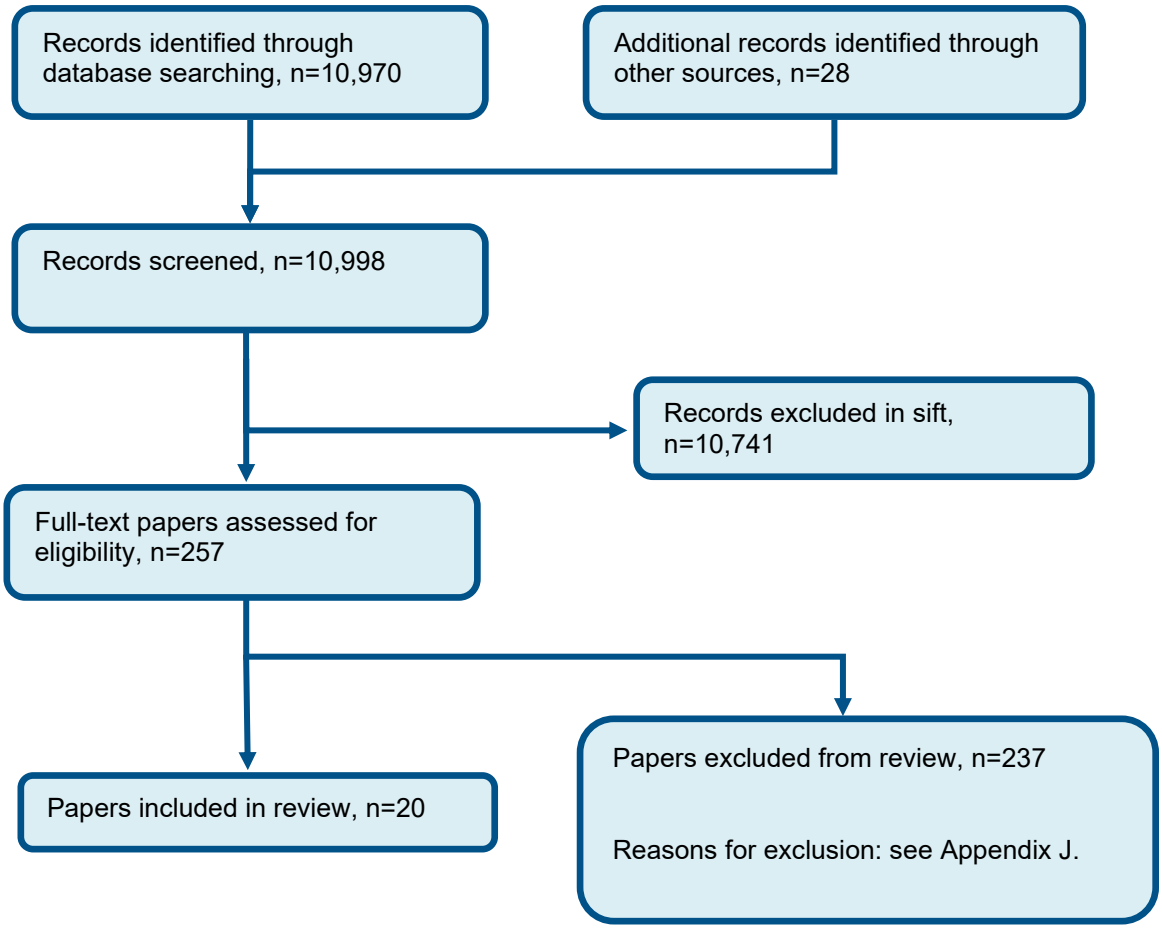
#1.	MeSH DESCRIPTOR Heart Valve Diseases EXPLODE ALL TREES
#2.	MeSH DESCRIPTOR Heart Valves EXPLODE ALL TREES
#3.	(((primary or secondary) adj Valv* adj disease*))
#4.	(((valv* or flap* or leaflet*) adj (heart or cardiac) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)))
#5.	((heart or cardiac) adj (valv* or flap* or leaflet*) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*))
#6.	(((mitral or aortic or tricuspid or pulmon*) adj (valv* or flap* or leaflet*) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)))
#7.	(((mitral or aortic or tricuspid or pulmon*) adj3 (prolapse or regurgitation or stenos?s or atresia or insufficienc*)))
#8.	MeSH DESCRIPTOR Heart Valve Prosthesis EXPLODE ALL TREES
#9.	(((mechanical or artificial or prosthe* or bioprosthe* or biological or tissue) adj (valv* or flap* or leaflet*)))
#10.	(valve-in-valve)
#11.	((transcatheter adj2 (valve or valves)))
#12.	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11

2

3

Appendix C –Prognostic evidence study selection

Figure 1: Flow chart of clinical study selection for the review of stress testing and stress echocardiography in determining need for intervention



1 Appendix D –Prognostic evidence

D.1 Asymptomatic severe aortic stenosis

Reference	Amato 2001[6]
Study type and analysis	Prospective cohort study between February 1987 and February 1992. Cox proportional hazards regression analysis Brazil
Number of participants and characteristics	N=66 Positive exercise test, n=44 Negative exercise test, n=22 Asymptomatic severe aortic stenosis **Inclusion criteria:** Severe aortic stenosis with aortic valve area ≤1cm^2 without coexisting valve disease **Exclusion criteria:** Symptoms characteristic of aortic valve disease (dyspnoea, angina pectoris, syncope, arrhythmias, and a range of minor symptoms, including dizziness, weakness, fatigue and exercise intolerance) and symptoms of other chronic conditions, to ensure that patients were in the latent period of aortic stenosis; arrhythmia, left bundle branch block or ST-T segment depression determined by ECG; coronary artery disease or other heart disease determined by cardiac catheterisation no longer than 6 months before study enrolment; comorbid disease associated with symptoms that could affect clinical evaluation and prevent exercise testing **Values listed below are presented as mean (SD) or number (%)** **Patient characteristics:** • Age: 49.7 (14.9) years (range, 18-80 years) • Male/female: 44/22 (66.7%/33.3%) • Aortic valve area: 0.61 (0.17) cm^2

Reference	Amato 2001[6]

	• Transaortic pressure gradient: 83.3 (33.0) mmHg
	• ST segment depression 0.08 seconds after J point: 1.42 (1.63) mm
	• Rise of systolic blood pressure from baseline (unclear if on exercise or at end of study): 26.40 (18.23) mmHg
	
	Exercise testing:
	• Negative: 22 (33.3%)
	• Positive: 44 (66.7%)
	  ○ Symptoms (3 arrhythmias): 7 (15.91%)
	  ○ Y point (0.08 seconds after J point in the ST segment depression): 8 (18.18%)
	  ○ Change in systolic blood pressure from baseline: 4 (9.09%)
	  ○ Symptoms + change in systolic blood pressure from baseline: 10 (22.73%)
	  ○ Symptoms + Y point (0.08 seconds after J point in the ST segment depression): 3 (6.82%)
	  ○ Y point (0.08 seconds after J point in the ST segment depression) + change in systolic blood pressure from baseline: 9 (20.45%)
	  ○ Symptoms + Y point (0.08 seconds after J point in the ST segment depression) + change in systolic blood pressure from baseline: 3 (6.82%)
	
	Population source: patients from single outpatient valve disease service between February 1987 and February 1992 prospectively identified and included in the study. Patients on their first visit to the service included. Consecutive patients matching criteria.

Prognostic variable	Positive exercise test Negative exercise test (referent) A positive exercise test was defined as any of the following observed on exercise testing: horizontal or downsloping ST segment depression of ≥1 mm in men or ≥2 mm in women, or an upsloping ST segment depression of ≥3 mm in men, measured 0.08 seconds after the J point (upsloping ST segment depression in women was considered negative); symptoms of aortic stenosis (precordial chest pain or near syncope); complex ventricular arrhythmia on ECG; or no rise in systolic blood pressure by ≥20 mmHg compared with baseline. Exercise testing was performed using a treadmill. The Ellestad protocol was used. 12-lead ECG, heart rate and systolic and diastolic blood pressure were recorded with the patients in standing position at rest and after 2 min of each stage of exercise protocol, and at peak exercise. Three-lead ECG was monitored continuously. Variables were recorded every 2 min after exercise for at least 6 min or until ST segment returned to baseline, blood pressure recovered, and symptoms disappeared. Exercise was interrupted when the rest was positive or when patient reached age-related maximum heart rate.

Reference	Amato 2001[6]
Confounders	Variables that demonstrated significance were included in the multivariate analysis: age, aortic valve area and exercise testing. Key confounders in protocol: coronary disease accounted for as was an exclusion criterion of the study, however remaining confounders not considered in the MV analysis or reported in study characteristics. Arthritis, lung disease/respiratory insufficiency and peripheral vascular disease may have been excluded based on the other comorbid conditions that were excluded, but this is unclear as a list of these is not provided.
Outcomes and effect sizes	**Appearance of symptoms in daily life or sudden death – medically managed** **HR 7.60 (95% CI 2.34 to 24.63) for positive vs. negative exercise test result** Note: study reports that it is a 'risk ratio', but Cox proportional hazards regression used suggests it should be a hazard ratio and so has been reported as a hazard ratio. No mention of surgery during the follow-up so assumed to be medically managed. Of those reaching an end-point in the study, 92.1% had a positive exercise test and 7.9% had a negative exercise test. After 24 months, the probability of someone with a positive test surviving without symptoms was 0.19 compared with 0.85 in those with a negative exercise test. Range of follow-up: 2.62-57.6 months. Mean (SD) follow-up: 14.77 (11.93) months. Physical examination and interview to detect symptoms typical of aortic stenosis (precordial chest pain, signs of heart failure, dizziness or syncope) were performed in patients every 3 months during the study.
Comments, risk of bias and indirectness	Risk of bias: 1. Study participation HIGH 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement HIGH 5. Study confounding HIGH 6. Statistical analysis LOW 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH Indirectness:

Reference	Amato 2001[6]
	• Prognostic factor – combination of various prognostic factors listed in the protocol, rather than providing prognostic information for each one separately (symptoms on exercise, reduction in BP >20 mmHg, ST depression and complex ventricular arrhythmia) • Confounding factors – coronary disease excluded from study but unclear whether other key confounders listed were also excluded or may have differed between groups (downgraded for this in risk of bias so not downgraded further for indirectness)

1

Reference	Capoulade 2014[32]
Study type and analysis	Prospective cohort study Cox proportional hazards multivariate analysis Canada, Belgium
Number of participants and characteristics	N= 157 (results reported for the severe AS subgroup, total study n=211) Absolute difference of BNP levels (per 100 pg/ml increase from rest), n=157 included in analysis as a continuous variable The study reports on moderate or severe asymptomatic AS but gives results separately for the severe AS subgroup, therefore results for this subgroup have been extracted in line with the protocol. **Inclusion criteria:** Asymptomatic; moderate to severe aortic stenosis (peak aortic jet velocity >2.5 m/s and aortic valve area <1.5 cm^2); and preserved left ventricular ejection fraction. **Exclusion criteria:** Moderate to severe aortic regurgitation or mitral valve disease; pregnant or lactating women; abnormal exercise test as previously defined; and estimated glomerular filtration rate <60 ml/min (MDRD formula). **Values listed below are presented as mean (SD) or number (%).**

Reference	Capoulade 2014[32]
	Note that patient characteristics are for the whole cohort (moderate or severe asymptomatic AS) as they were not given separately for the severe subgroup. • Patient characteristics: • Age: 68 (11) years • Male gender: 64% • Body surface area: 1.82 (0.18) m2 • Body mass index: 26.6 (3.7) kg/m^2 • Heart rate: 70 (12) beats/min • History of hypertension, 53% • Systolic blood pressure: 141 (21) mmHg • Diastolic blood pressure: 77 (11) mmHg • Hypercholesterolaemia, 46% • Diabetes, 14% • History of smoking, 27% • Resting BNP level, median (IQR): 43 (24-81) pg/ml • Stroke volume: 84 (19) ml • Stroke volume index: 46 (11) ml/m^2 • Peak aortic jet velocity: 4.0 (0.7) m/s • Peak transvalvular gradient: 66 (24) mmHg • Mean transvalvular gradient: 41 (15) mmHg • Aortic valve area: 0.93 (0.21) cm^2 • Indexed aortic valve area: 0.51 (0.12) cm^2/m^2 • Indexed left atrial area: 11.6 (3.3) cm^2 • E to e': 10.8 (4.2) • Pulmonary hypertension, 3% • Relative wall thickness: 0.51 (0.12) • LV mass index: 124 (45) g/m^2 • LVEF: 66 (7)% • Valvulo-arterial impedance: 4.1 (1.1) mmHg/ml/m^2

Reference	Capoulade 2014[32]
	Exercise testing: values at peak exercise • Duration: 9.1 (3.1) min • Peak exercise workload: 99 (35) watts • Peak exercise heart rate: 120 (19) beats/min • Percentage of predicted maximal heart rate: 91 (12)% • Peak exercise systolic blood pressure: 179 (23) mmHg • Peak exercise diastolic blood pressure: 87 (14) mmHg • Peak exercise BNP level, median (IQR): 58 (29-115) pg/ml • Stroke volume: 94 (29) ml • Stroke volume index: 49 (16) ml/m^2 • Peak aortic jet velocity: 4.6 (0.8) m/s • Peak transvalvular gradient: 86 (28) mmHg • Mean transvalvular gradient: 53 (19) mmHg • Aortic valve area: 1.01 (0.29) cm^2 • Indexed aortic valve area: 0.56 (0.16) cm^2/m^2 • Pulmonary hypertension, 32% • LVEF: 68 (9)% • Valvulo-arterial impedance: 5.1 (1.9) mmHg/ml/m^2 **Population source:** Patients recruited from two centres in Quebec and Liège. Unclear if consecutive. Time period recruited across unclear.
Prognostic variable	Absolute difference of BNP levels (per 100 pg/ml increase from rest) as a continuous measure. Exercise testing: Symptom-limited graded bicycle test was performed in semi-supine position on a dedicated tilting exercise table. Doppler echocardiographic data were obtained at rest and at peak exercise. Plasma BNP levels were taken before echocardiography after 20 min of supine rest and at peak exercise, within 3 min after the end of exercise.
Confounders	Traditional risk factors of the composite of death or aortic valve replacement and all variables with P<0.10 in univariate analyses (age, gender, resting mean gradient, resting valvulo-arterial impedance, resting indexed left atrial area, resting BNP level and exercise-induced increases in heart rate, mean gradient and valvulo-arterial impedance) were included in the multivariate analysis.

Reference	Capoulade 2014[32]
	Key confounders in protocol: none of those listed in protocol included as confounders in the MV analysis or excluded from the study. None mentioned in study characteristics tables either.
Outcomes and effect sizes	**Death or aortic valve replacement indicated by development of symptoms or LV dysfunction – medically managed as AVR included as part of the composite outcome** **HR 3.4 (95% CI 2.2 to 5.3) for absolute difference of BNP levels (per 100 pg/ml increase from rest) as a continuous measure.** Note: to ensure blinding, resting and peak exercise BNP levels were not revealed to treating physician or surgeon A total of 87 events occurred in the severe subgroup (n=7 deaths and n=78 aortic valve replacements), leading to a cardiac event-free survival of 72±4%, 48±5% and 39±5% at 1, 2 and 3 years, respectively. Mean (SD) follow-up for severe subgroup: 1.5 (1.2) years.
Comments, risk of bias and indirectness	Risk of bias: 1. Study participation HIGH 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement LOW 5. Study confounding HIGH 6. Statistical analysis HIGH 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH Indirectness: • Prognostic factor – difference between exercise and rest BNP levels as a continuous variable, rather than a dichotomous increase in BNP levels vs. no increase in BNP levels on exercise compared with rest • Confounders – have not adjusted for any of the pre-specified confounders listed in the protocol or mentioned them as exclusion criteria so these factors may be contributing to the results (downgraded for this in risk of bias so not downgraded further for indirectness)

1

Reference	Chambers 2019[36]
Study type and analysis	Retrospective cohort study EXTAS study

Reference	Chambers 2019[36]
	Cox proportional hazards model UK
Number of participants and characteristics	N=102 (severe subgroup only) or N=306 (moderate or severe groups making up total cohort) <u>Whole cohort: moderate or severe AS</u> Abnormal BP response (sustained reduction of systolic BP ≥20 mmHg below previous stage or baseline level), n=113 Normal BP response, n=193 **Note: for revealed symptoms outcome this is limited to population that were asymptomatic on baseline exercise test and numbers with/without abnormal BP response are not given for this subgroup.** <u>Severe AS:</u> Abnormal BP response (sustained reduction of systolic BP ≥20 mmHg below previous stage or baseline level), n=42 Normal BP response, n=60 The study reports on asymptomatic moderate or severe aortic stenosis but results have been given separately for the severe subgroup for certain outcomes, therefore, results for this subgroup have been extracted in line with the protocol. The whole cohort data has been used for other outcomes matching the protocol where separate data for the severe subgroup have not been provided. **Inclusion criteria:** Age >18 years; moderate (effective orifice area 1.0-1.6 cm^2) or severe (effective orifice area <1.0 cm^2) aortic stenosis; apparently asymptomatic on their history and eligible for exercise treadmill testing. **Exclusion criteria:** Presence of spontaneous symptoms justifying surgery; more than moderate disease of other valves; chronic obstructive pulmonary disease; peripheral vascular disease; skeletal disorders; anaemia; peak heart rate not recorded on exercise testing. **Values listed below are presented as mean (SD) or number (%)** **Patient characteristics:**

Reference	Chambers 2019[36]

	Whole cohort: moderate or severe AS – used for revealed symptoms outcome in the subgroup that remained asymptomatic on baseline exercise testing. Note that details are not given separately for this subgroup of 219 participants.
	• Age: 65 (12) years
	• % male: 67%
	• Severity of valve disease:
	  ○ Moderate, 66.7%
	  ○ Severe, 33.%
	• Obesity, 26%
	• Smoker, 48%
	• Coronary artery disease, 50%
	• Diabetes mellitus, 14%
	• Previous stroke or transient ischaemic attack, 12%
	• Atrial fibrillation, 14%
	• Hypercholesterolaemia, 66%
	• Clinic systolic BP: 142 (19) mmHg
	• Clinic diastolic BP: 82 (13) mmHG
	• Hypertension, 73%
	• Antihypertensive treatment, 65%
	  ○ Beta-blockers, 33%
	  ○ Diuretics, 30%
	  ○ Calcium blockers, 26%
	  ○ ACE inhibitors, 20%
	  ○ ARB inhibitors, 12%
	  ○ Alpha-blockers, 8%
	• LV end-diastolic diameter: 4.6 (0.7) cm
	• Interventricular septal thickness: 1.29 (0.26) cm
	• Posterior wall thickness: 1.12 (0.22) cm
	• LV mass index: 52 (17) g/m$^{2.7}$
	• LV hypertrophy, 54%
	• LV ejection fraction: 60 (7)%
	• Peak aortic jet velocity: 3.7 (0.6) m/s

Reference	Chambers 2019[36]

	• Mean aortic gradient: 34 (13) mmHg
	• Effective orifice area: 0.94 (0.22) cm^2
	• Doppler stroke volume index: 43 (13) ml/m^2
	• Pulse pressure/stroke volume index: 1.46 (0.57) $mmHg/ml/m^2$
	• Valvulo-arterial impedance: 4.37 (1.25) $mmHg/ml/m^2$
	• LV stroke work: 159.9 (52.7) g-m/bpm
	
	<u>Severe AS: used for AVR outcome</u>
	• Age: 69 (11) years
	• Male: 61%
	• Obesity, 25%
	• Smoker, 50%
	• Coronary artery disease, 35%
	• Diabetes mellitus, 12%
	• Previous stroke or transient ischaemic attack, 9%
	• Atrial fibrillation, 21%
	• Hypercholesterolaemia, 57%
	• Clinic systolic BP: 145 (21) mmHg
	• Clinic diastolic BP: 86 (11) mmHG
	• Hypertension, 65%
	• Antihypertensive treatment, 65%
	  ○ Beta-blockers, 35%
	  ○ Diuretics, 28%
	  ○ Calcium blockers, 29%
	  ○ ACE inhibitors, 11%
	  ○ ARB inhibitors, 10%
	  ○ Alpha-blockers, 6%
	• LV end-diastolic diameter: 4.5 (0.7) cm
	• Interventricular septal thickness: 1.35 (0.28) cm
	• Posterior wall thickness: 1.15 (0.26) cm

Reference	Chambers 2019[36]
	• LV mass index: 55 (20) g/m$^{2.7}$ • LV hypertrophy, 59% • LV ejection fraction: 60 (6)% • Peak aortic jet velocity: 4.4 (0.5) m/s • Mean aortic gradient: 47 (12) mmHg • Effective orifice area: 0.74 (0.14) cm^2 • Doppler stroke volume index: 41 (10) ml/m^2 • Pulse pressure/stroke volume index: 1.50 (0.60) mmHg/ml/m^2 • Valvulo-arterial impedance: 4.85 (1.19) mmHg/ml/m^2 • LV stroke work: 157.9 (44.7) g-m/bpm **Exercise testing:** Whole cohort – moderate or severe AS – used for revealed symptoms outcome in the subgroup that remained asymptomatic on baseline exercise testing. Note that details are not given separately for this subgroup of 219 participants. • Pre-exercise heart rate: 77 (15) bpm • Pre-exercise systolic BP: 141 (19) mmHg • Pre-exercise diastolic BP: 85 (11) mmHg • Peak heart rate: 134 (25) bpm • Peak systolic BP: 166 (26) mmHg • Peak diastolic BP: 90 (16) mmHg • Abnormal BP response, 37% (n=113) • Target heart rate achieved: 86 (15)% • Rapid early rise in heart rate, 25% • Exercise duration: 9.7 (4.4) min • Metabolic equivalents: 8.5 (4.5) • Revealed symptoms, 28.4% • Double product: 1.90 (0.46) mmHg/bpm Severe AS: used for AVR outcome • Pre-exercise heart rate: 78 (16) bpm

Reference	Chambers 2019[36]
	• Pre-exercise systolic BP: 143 (19) mmHg • Pre-exercise diastolic BP: 86 (11) mmHg • Peak heart rate: 134 (23) bpm • Peak systolic BP: 165 (25) mmHg • Peak diastolic BP: 91 (16) mmHg • Abnormal BP response, 41% (n=42) • Target heart rate achieved: 89 (14)% • Rapid early rise in heart rate, 28% • Exercise duration: 9.6 (3.6) min • Metabolic equivalents: 8.0 (3.9) • Revealed symptoms, 36.3% • Double product: 1.90 (0.43) mmHg/bpm **Population source:** Retrospective cohort study of data collected prospectively between January 2000 and May 2017 at a single specialist heart valve clinic at Guy's and St Thomas' Hospital in the UK. Likely to be consecutive matching criteria but unclear.
Prognostic variable	Abnormal BP response to exercise (sustained reduction of systolic BP ≥20 mmHg below previous stage or baseline level) Normal BP response to exercise (referent) Exercise testing: Exercise treadmill testing performed using Bruce protocol that was modified by two warm-up stages so that most patients of any age can exercise for 9 min, equivalent to 3 min of a standard Bruce protocol. Test was stopped early for symptoms (significant breathlessness or any chest constriction or dizziness), progressive ventricular ectopy >3 beats, new atrial fibrillation, a sustained fall in systolic blood pressure >20 mmHg from previous stage or >5 mm ST segment depression). Significant symptoms (breathlessness, chest tightness, dizziness, presence of distress, inability to speak and facial pallor) were differentiated clinically from physiological breathlessness at high workload.
Confounders	The following variables were included in the multivariate analysis: rapid early rise in heart rate, age, sex, hypertension, Doppler stroke volume, mean pressure gradient, abnormal blood pressure response and coronary artery disease. Key confounders in protocol: of those listed in the protocol, one was excluded from the study (peripheral vascular disease), another was partially excluded from the study (lung disease/respiratory insufficiency – COPD reported to be excluded but unclear whether other lung comorbidities were) and one was included in the MV analysis (coronary artery disease). Arthritis, the remaining confounder listed in the protocol, was not mentioned.

Reference	Chambers 2019[36]
Outcomes and effect sizes	**<u>Revealed symptoms developing spontaneously or during follow-up – subgroup of 219 patients with moderate or severe AS that remained asymptomatic on baseline exercise testing – medically managed as no indication for surgery unless symptoms revealed</u>** **HR 1.87 (95% CI 0.93 to 3.79) for abnormal vs. normal BP response to exercise** Note: though results were reported for this subgroup, patient characteristics were not reported separately for this group and the number with/without abnormal BP response in this subgroup is not reported. **<u>Aortic valve replacement – subgroup of 102 patients with severe asymptomatic AS at baseline (prior to exercise testing) – medically managed up until indication for aortic valve replacement developed</u>** **HR 1.86 (95% CI 1.00 to 3.44) for abnormal vs. normal BP response to exercise** During follow-up in whole cohort, 254 (84%) patients experienced an event, including 226 aortic valve replacements and 28 deaths. These details not reported separately for the severe subgroup or the subgroup with moderate or severe AS that did not develop symptoms on baseline exercise testing. Mean (SD) follow-up for the whole cohort: 34.9 (34.6) months. Not reported separately for the different severities.
Comments, risk of bias and indirectness	Risk of bias: <u>Revealed symptoms outcome:</u> 1. Study participation — LOW 2. Study attrition — LOW 3. Prognostic factor measurement — LOW 4. Outcome Measurement — HIGH 5. Study confounding — HIGH 6. Statistical analysis — HIGH 7. Other risk of bias — LOW OVERALL RISK OF BIAS — VERY HIGH <u>Aortic valve replacement outcome:</u> 1. Study participation — LOW 2. Study attrition — LOW 3. Prognostic factor measurement — LOW 4. Outcome Measurement — HIGH

Reference	Chambers 2019[36]	
	5. Study confounding	HIGH
	6. Statistical analysis	HIGH
	7. Other risk of bias	LOW
	OVERALL RISK OF BIAS	VERY HIGH
	Indirectness: <u>Revealed symptoms outcome:</u> • Population – includes moderate or severe AS patients that were asymptomatic at baseline and remained asymptomatic on baseline exercise testing, not limited to asymptomatic severe AS • Confounders – though three of the four pre-specified confounders have been accounted for in some way, arthritis, the final confounder was not mentioned (downgraded for this in risk of bias so not downgraded further for indirectness) <u>Aortic valve replacement outcome:</u> • Confounders – though three of the four pre-specified confounders have been accounted for in some way, arthritis, the final confounder was not mentioned (downgraded for this in risk of bias so not downgraded further for indirectness)	

1

Reference	Das 2005[51]
Study type and analysis	Prospective cohort study Multivariate logistic regression model UK
Number of participants and characteristics	N=125 Limiting symptoms on exercise, n=46 No limiting symptoms on exercise, n=79 Abnormal blood pressure response (decrease or no increase in resting BP on exercise), n=29 Normal blood pressure response, n=96 ST depression ≥2 mm on exercise, n=33

Reference	Das 2005[51]
	ST depression <2 mm on exercise, n=92 Note: unclear if coronary disease absent – it was prespecified in the protocol that for this prognostic factor, absence of coronary disease is important Asymptomatic aortic stenosis (mild to severe, but majority, 92%, were moderate or severe). Aortic stenosis was graded by continuity effective orifice area at rest: mild (area >1.2 cm^2); moderate (area 0.8-1.2 cm^2); and severe (≤0.8 cm^2). **Inclusion criteria:** Aortic valve thickening; effective orifice area <1.4 cm^2; normal left ventricular systolic function (fractional shortening >28% and no regional wall abnormality). **Exclusion criteria:** More than mild aortic regurgitation; other significant valve disease; known pulmonary disease. **Values listed below are presented as) mean (SD) or number (%)** **Patient characteristics:** • Mean (range) age: 65 (56-74) years • Male/female, 85/40 (68%/32%) • Specific Activity Scale questionnaire class I/II, 72%/28% • Peak velocity: 3.8 (0.8) m/s • Mean pressure drop: 36.0 (16.1) mmHg • Effective orifice area: 0.9 (0.2) cm^2 **Exercise testing:** • Exercise time: 10.9 (3.7) min • Limiting symptoms, 36.8% • Systolic BP increase: 19.4 (19.7) mmHg • Abnormal blood pressure response, 23.2% • ST depression ≥2 mm, 26.4%

Reference	Das 2005[51]
	Population source: Recruited from echocardiography department at single centre in the UK between August 1996 and December 2001. Likely to be consecutive matching inclusion criteria but not explicitly stated.
Prognostic variable	Limiting symptoms on exercise No limiting symptoms on exercise (referent) Abnormal blood pressure response (decrease or no increase in resting BP on exercise) Normal blood pressure response (referent) ST depression ≥2 mm on exercise ST depression <2 mm on exercise (referent) Exercise testing: Performed using a Bruce protocol modified by two warm-up stages and a treadmill. Subjects were questioned for symptoms every 2 min at the heart rate, blood pressure and 12-lead ECG were recorded at baseline, at the end of each stage and at peak exercise. An exercise test was positive if stopped early due to limiting breathlessness/chest discomfort or dizziness. Each patient was questioned and observed carefully to distinguish between significant breathlessness or chest restriction associated with distress from rapidly reversible minor breathlessness. Other criteria for early stopping of exercise testing were ST segment depression >5 mm measured 80 ms after the J point, >3 consecutive ventricular premature beats and hypotension (fall in systolic blood pressure >20 mmHg compared with baseline). Otherwise, the test continued until the patient was fatigued. ST depression ≥2 mm in a single lead was considered significant. An abnormal blood pressure response was a systolic blood pressure at peak exercise that was the same or below the baseline level.
Confounders	Variables that demonstrated significance in univariate analyses were included in the multivariate analysis: total exercise time, exercise-limiting symptoms, peak transaortic velocity, effective orifice area, abnormal blood pressure response and ST segment depression. Key confounders in protocol: none of those prespecified in protocol were included in the multivariate analysis, however pulmonary disease (lung disease/respiratory insufficiency) was an exclusion criterion for this study. The remaining three confounders not adjusted for and may differ between the prognostic groups.
Outcomes and effect sizes	**Development of spontaneous exertional symptoms or cardiovascular death within 12 months of initial study – medically managed, not explicitly stated but no mention of aortic valve surgery being performed** **OR 7.73 (95% CI 2.79 to 21.39) for limiting symptoms vs. no limiting symptoms on exercise** **OR 1.02 (95% CI 0.98 to 1.05) for abnormal blood pressure response vs. normal blood pressure response to exercise**

Reference	Das 2005[51]
	OR 0.97 (95% CI 0.95 to 1.02) for ST depression ≥2 mm vs. ST depression <2 mm on exercise Note: in 4 cases, ECG changes were uninterpretable due to resting bundle branch block or left ventricular hypertrophy. Study appears to have counted these as showing <2 mm ST depression. During follow-up, 36 (29%) developed spontaneous symptoms and there were no deaths reported within the 12 months. Follow-up was 12 months in all patients.
Comments, risk of bias and indirectness	Risk of bias: <u>For limiting symptoms prognostic factor</u> 1. Study participation HIGH 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement HIGH 5. Study confounding HIGH 6. Statistical analysis HIGH 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH <u>For abnormal BP response prognostic factor</u> 1. Study participation HIGH 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement HIGH 5. Study confounding HIGH 6. Statistical analysis HIGH 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH <u>For ST depression ≥2 mm prognostic factor</u> 1. Study participation HIGH

Reference	Das 2005[51]	
	2. Study attrition	LOW
	3. Prognostic factor measurement	LOW
	4. Outcome Measurement	HIGH
	5. Study confounding	HIGH
	6. Statistical analysis	HIGH
	7. Other risk of bias	LOW
	OVERALL RISK OF BIAS	VERY HIGH

Indirectness:

<u>For limiting symptoms prognostic factor</u>

- Population – includes asymptomatic mild to severe AS, but majority are either moderate or severe (92%). Only 42% of the population represented asymptomatic severe AS as specified in the protocol.
- Confounders – though lung disease was an exclusion criterion, have not adjusted for the three remaining pre-specified confounders listed in the protocol so these factors may be contributing to the results (downgraded for this in risk of bias so not downgraded further for indirectness)

<u>For abnormal BP response prognostic factor</u>

- Population – includes asymptomatic mild to severe AS, but majority are either moderate or severe (92%). Only 42% of the population represented asymptomatic severe AS as specified in the protocol.
- Confounders – though lung disease was an exclusion criterion, have not adjusted for the three remaining pre-specified confounders listed in the protocol so these factors may be contributing to the results (downgraded for this in risk of bias so not downgraded further for indirectness)

<u>For ST depression ≥2 mm prognostic factor</u>

- Population – includes asymptomatic mild to severe AS, but majority are either moderate or severe (92%). Only 42% of the population represented asymptomatic severe AS as specified in the protocol.
- Prognostic factor – unclear if coronary disease is absent, which was specified in the protocol as important when this prognostic factor was used.
- Confounders – though lung disease was an exclusion criterion, have not adjusted for the three remaining pre-specified confounders listed in the protocol so these factors may be contributing to the results (downgraded for this in risk of bias so not downgraded further for indirectness)

1

Reference	Lancellotti 2010-1[122]
Study type and analysis	Prospective cohort study Cox proportional hazards regression Belgium **Note that there may be overlap between the results of this paper and the other Lancellotti 2010 paper included, as the number of events reported are very similar. Some of the same patients may be included in both papers but the analysis differs slightly.**
Number of participants and characteristics	N=163 Abnormal exercise test, n=69 Normal exercise test, n=94 Asymptomatic significant AS (moderate or severe – aortic valve area ≤0.6 cm^2/m^2) **Inclusion criteria:** Moderate to severe AS (aortic valve area ≤0.6 cm^2/m^2); absence of symptoms; normal left ventricular ejection fraction (≥55%) based on 2D echocardiography; and in sinus rhythm. **Exclusion criteria:** More than mild concomitant valve disease; and patients with <1-year clinical follow-up. **Values listed below are presented as mean (SD) or number (%)** **Patient characteristics:** • Age: 70 (10) years • Male sex, 65% • Overweight, 48 (29%) • Hypertension, 81 (50%) • Diabetes mellitus, 27 (17%) • Hypercholesterolaemia, 72 (44%)

Reference	Lancellotti 2010-1[122]
	• Current smoking, 45 (28%) • Serum creatinine: 8.7 (1.9) mg/l • Systolic arterial pressure: 142 (18) mmHg • Diastolic arterial pressure: 76 (11) mmHg • Systemic arterial compliance: 0.7 (0.3) ml/mm Hg/m^2 • Indexed aortic valve area: 0.45 (0.09) cm^2/m^2 • Peak aortic velocity: 4.2 (0.6) m/s • Mean pressure gradient: 46 (14) mmHg • Valvulo-arterial impedance: 4.4 (1.3) mmHg ml/m^2 • LV mass: 91 (45) g/m^2 • LV end-diastolic diameter: 42 (12) mm • LV end-diastolic volume: 100 (133) ml • LV end-systolic volume: 35 (19) ml • LV ejection fraction: 66 (9)% • Midwall fractional shortening: 21 (10)% • LV longitudinal strain: 15.7 (3.1)% • LA area index: 12.4 (3.5) cm^2/m^2 • Mitral E wave: 0.83 (0.27) m/s • Mitral A wave: 0.91 (0.29) m/s • Mitral E/A ratio: 0.99 (0.54) **Exercise testing:** • Abnormal response to exercise, 69 (42%) **Population source:** Consecutive patients with asymptomatic significant aortic stenosis between January 2000 and December 2007 at a single hospital site in Belgium.

Reference	Lancellotti 2010-1[122]
Prognostic variable	Abnormal exercise test (defined below) Normal exercise test (referent) Exercise testing: symptom-limited graded bicycle test performed in all patients. Initial workload of 25W maintained for 2 min, followed by increases of 25W every 2 min. 12-lead ECG monitored continuously. Test was interrupted when age-related maximum heart rate was reached or for any of the following: development of symptoms (angina, dyspnoea); fall in blood pressure; or ventricular arrhythmias. The test was considered abnormal if patients presented with any of the following: angina; evidence of dyspnoea, dizziness, syncope or near syncope; ≥2 mm ST segment depression relative to baseline; rise in systolic blood pressure during exercise <20 mmHg or a fall in blood pressure; or complex ventricular arrhythmias.
Confounders	Clinically relevant variables that achieved a P-value <0.1 on univariate analysis were included in the multivariate analyses performed. The following appear to have been included in the multivariate analysis: gender; systemic arterial compliance; peak aortic velocity; valvulo-arterial impedance; LV longitudinal strain; LA area index; mitral E wave; mitral E/A ratio; and abnormal exercise test result. Key confounders in protocol: none of the prespecified confounders in the protocol included in the multivariate analysis or listed as exclusion criteria for the study.
Outcomes and effect sizes	**Development of significant symptoms, need for aortic valve replacement or cardiac-related death** **HR 1.1 (95% CI 0.6 to 2.0) for abnormal vs. normal exercise test** Note: follow-up was censored at time of cardiac surgery if eventually performed. Significant symptoms are defined as angina, dyspnoea, syncope or heart failure). During follow-up, end-points occurred in 74 patients (n=6 cardiac deaths, n=57 need for AVR and n=11 developing symptoms that did not have AVR). For the cardiac deaths, n=3 were due to congestive heart failure related to AS and n=3 were sudden deaths without preceding symptoms. The following additional deaths occurred: n=1 postoperatively due to endocarditis and n=1 due to cancer. AVR was required due to development of symptoms in n=44 patients within 15 (13) months follow inclusion. Predominant symptoms were severe dyspnoea, angina or syncope in 26, 6 and 3 patients, respectively. 9 patients developed both angina and dyspnoea. Of the other 13 patients, surgery was performed due to onset of severely symptomatic atrial fibrillation in 1 patient, a newly positive exercise test during follow-up in 6 patients and equivocal symptoms in 6 patients. In total, 89 patients were free of clinical events after a follow-up of 26±22 months. Range of follow-up: 4-102 months. Mean (SD) follow-up: 20 (19) months.
Comments, risk of bias and indirectness	Risk of bias: 1. Study participation HIGH 2. Study attrition HIGH

Reference	Lancellotti 2010-1[122]	
	3. Prognostic factor measurement	LOW
	4. Outcome Measurement	HIGH
	5. Study confounding	HIGH
	6. Statistical analysis	HIGH
	7. Other risk of bias	LOW
	OVERALL RISK OF BIAS	VERY HIGH
	Indirectness: • Population – not limited to asymptomatic severe AS as includes some with asymptomatic moderate AS. • Prognostic factor – combination of various prognostic factors listed in the protocol, rather than providing prognostic information for each one separately (symptoms on exercise, rise in systolic BP <20 mmHg or fall in BP on exercise, ST depression ≥2 mm and complex ventricular arrhythmia) • Confounders – have not adjusted for any of the pre-specified confounders listed in the protocol or mentioned them as exclusion criteria so these factors may be contributing to the results (downgraded for this in risk of bias so not downgraded further for indirectness)	

1

Reference	Lancellotti 2010-2[132]
Study type and analysis	Prospective cohort study Cox proportional hazards regression Belgium **Note that there may be overlap between the results of this paper and the other Lancellotti 2010 paper included, as the number of events reported are very similar. Some of the same patients may be included in both papers but the analysis differs slightly.**
Number of participants and characteristics	N=126 Abnormal exercise test, n=32 Normal exercise test, n=94

Reference	Lancellotti 2010-2[132]
	Asymptomatic significant AS (moderate or severe – aortic valve area ≤1.2 cm^2) **Inclusion criteria:** Moderate to severe AS (aortic valve area ≤1.2 cm^2); no symptoms according to history by referring physician; normal left ventricular ejection fraction (≥55%) based on 2D echocardiography; in sinus rhythm; and serum creatinine <16 mg/l. **Exclusion criteria:** More than mild concomitant valve disease. **Values listed below are presented as mean (SD) or number (%)** **Patient characteristics:** • Age: 67.51 (11.04) years. Range 41-84 years. • Male sex, 59.5% • Hypertension, 61 (48.4%) • Diabetes mellitus, 24 (19%) • Hypercholesterolaemia, 54 (42.9%) • Serum creatinine: 8.45 (1.77) mg/l • Systolic arterial pressure: 142.5 (18.56) mmHg • B-type natriuretic peptide: 101.9 (68.04) • Aortic valve area: 0.83 (0.15) cm^2 • Peak aortic velocity: 4.19 (0.59) m/s • Mean pressure gradient: 44.52 (13.38) mmHg • Peak pressure gradient: 73.29 (20.67) mmHg • LV mass: 171.5 (77.28) g • LV end-diastolic volume: 94.82 (28.51) ml • LV end-systolic volume: 32.35 (13.62) ml • LV ejection fraction: 66.59 (7.49)% • LA area index: 12.51 (3.60) cm^2/m^2 • Mitral early diastolic filling wave: 79.95 (25.18) cm/s

Reference	Lancellotti 2010-2[132]
	• Mitral late diastolic filling wave: 87.98 (28.53) cm/s • Mitral early/late filling ratio: 0.95 (0.41) • Mitral earl diastolic filling wave deceleration time: 227.9 (88.32) ms • Peak systolic velocity: 4.41 (1.52) cm/s • Peak early diastolic annular velocity: 8.94 (2.03) cm/s • Peak late diastolic annular velocity: 8.16 (2.12) cm/s • Early diastolic filling/annular velocity (average annuli): 11.72 (5.48) **Exercise testing:** • Abnormal response to exercise, 32 (25.4%) **Population source:** Patients with asymptomatic moderate to severe AS from single echocardiography laboratory. Unclear if consecutive. Time period unclear.
Prognostic variable	Abnormal exercise test (defined below) Normal exercise test (referent) Exercise testing: symptom-limited graded bicycle test performed in all patients. Initial workload of 25W maintained for 2 min, followed by increases of 25W every 2 min. 12-lead ECG monitored continuously. Test was interrupted when age-related maximum heart rate was reached or for any of the following: development of symptoms (angina, dyspnoea); hypotension; or significant ventricular arrhythmias. The test was considered abnormal if patients presented with any of the following: angina; evidence of dyspnoea, dizziness, syncope or near syncope; rise in systolic blood pressure during exercise <20 mmHg or a fall in blood pressure; or ventricular tachycardia or >4 premature ventricular complexes in a row.
Confounders	Clinically relevant variables that achieved a P-value <0.1 on univariate analysis were included in the multivariate analyses performed. The following appear to have been included in the multivariate analysis: gender; B-type natriuretic peptide; abnormal response to exercise; aortic valve area; peak aortic velocity; aortic mean pressure gradient; left atrial area index; peak systolic velocity; peak early diastolic annular velocity; peak late diastolic annular velocity; and early diastolic filling/annular velocity. Key confounders in protocol: none of the prespecified confounders in the protocol included in the multivariate analysis or listed as exclusion criteria for the study.
Outcomes and effect sizes	**Development of symptoms, need for aortic valve replacement or cardiac-related death** **HR 0.95 (95% CI 0.49 to 1.80) for abnormal vs. normal exercise test**

Reference	Lancellotti 2010-2[132]
	Note: follow-up was censored at time of cardiac surgery if eventually performed. Symptoms are defined as angina, dyspnoea, syncope or heart failure). During follow-up, end-points occurred in 62 patients (n=6 cardiac deaths, n=48 need for AVR and n=8 developing symptoms that did not have AVR). For the cardiac deaths, n=3 were due to congestive heart failure related to AS and n=3 were sudden deaths. AVR was required due to development of symptoms in n=34 patients, new-onset atrial fibrillation in 1 patient, a newly positive exercise test during follow-up in 7 patients and equivocal symptoms in 6 patients. Median (SD) follow-up: 20.3 (18.7; IQR 9-22) months.
Comments, risk of bias and indirectness	Risk of bias: 1. Study participation HIGH 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement HIGH 5. Study confounding HIGH 6. Statistical analysis HIGH 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH Indirectness: • Population – not limited to asymptomatic severe AS as includes some with asymptomatic moderate AS. • Prognostic factor – combination of various prognostic factors listed in the protocol, rather than providing prognostic information for each one separately (symptoms on exercise, rise in systolic BP <20 mmHg or fall in BP on exercise and ventricular arrhythmia) • Confounders – have not adjusted for any of the pre-specified confounders listed in the protocol or mentioned them as exclusion criteria so these factors may be contributing to the results (downgraded for this in risk of bias so not downgraded further for indirectness)

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2

Reference	Marechaux 2010[160]
Study type and analysis	Prospective cohort study Cox proportional hazards model France, Canada, Belgium
Number of participants and characteristics	N=135 Increase in mean gradient >20 mmHg during exercise, n=28 Increase in mean gradient ≤20 mmHg during exercise (referent), n=107 Asymptomatic moderate or severe aortic stenosis – proportion with severe AS unclear **Inclusion criteria:** At least moderate aortic stenosis (aortic valve area <1.5 cm^2 and indexed aortic valve area <0.9 cm^2/m^2); undergoing exercise stress echocardiography. **Exclusion criteria:** Symptoms, including dyspnoea, angina, syncope or heart failure; LV ejection fraction <50%; moderate/severe aortic or mitral regurgitation, or mitral stenosis; coronary artery disease (history of myocardial infarction or coronary artery stenosis on coronary angiography); known pulmonary disease; atrial fibrillation or flutter; inability to perform physical exercise; and abnormal exercise test (breathlessness or fatigue at low workload, or angina, dizziness or syncope; fall in systolic blood pressure below baseline; or complex ventricular arrhythmia). **Values listed below are presented as mean (SD) or number (%)** **Patient characteristics:** • Age: 64 (15) years • Male sex, 87 (64%) • Body surface area: 1.8 (0.2) m^2 • Body mass index: 26 (4) kg/m^2 • Hypertension, 63 (47%) • Diabetes, 13 (10%) • Hypercholesterolaemia, 50 (37%)

Reference	Marechaux 2010[160]
	• Heart rate: 71 (12) bpm • Systolic blood pressure: 138 (21) mmHg • Bicuspid valve, 23 (17%) • LV mass index: 105 (34) g/m^2 • LV hypertrophy, 55 (41%) • LV ejection fraction: 65 (7)% • LV stroke volume: 83 (17) ml • Mean transvalvular flow rate: 269 (55) ml/s • Aortic valve area: 0.97 (0.22) cm^2 • Aortic valve area index: 0.53 (0.12) cm^2/m^2 • Peak aortic jet velocity: 3.8 (0.8) m/s • Peak pressure gradient: 61 (24) mmHg • Mean pressure gradient: 36 (15) mmHg **Exercise testing:** values at peak exercise • Heart rate: 126 (24) bpm • Systolic blood pressure: 178 (27) mmHg • Exercise duration: 13 (5) min • Peak workload, median (IQR): 90 (65-120) W • Percent workload, median (IQR): 73 (54-89)% • ST segment depression ≥2 mm, 14 (10%) • LV ejection fraction: 71 (10)% • LV stroke volume: 85 (22) ml • Mean transvalvular flow rate: 345 (87) ml/s • Aortic valve area: 1.07 (0.27) cm^2 • Aortic valve area index: 0.59 (0.14) cm^2/m^2 • Peak aortic jet velocity: 4.5 (0.8) m/s • Peak pressure gradient: 82 (27) mmHg • Mean pressure gradient: 49 (19) mmHg

Reference	Marechaux 2010[160]
	Population source: patients matching inclusion criteria across four locations (three European hospitals and one Canadian centre). Time period unclear. Unclear if consecutive but likely to be.
Prognostic variable	Increase in mean gradient >20 mmHg during exercise Increase in mean gradient ≤20 mmHg during exercise (referent) Exercise testing: symptom-limited graded maximum bicycle exercise test performed in semi-supine position on an ergometer table that was tilted. After an initial workload of 20-25 W for 3 min, workload was increased by 20-25 W every 3 min. 12-lead ECG was monitored continuously and blood pressure measured at rest and every 2 min during exercise. If patients were on beta-blockers, they were asked to stop the medication 24 h prior to the rest. Other medications were left unchanged. Doppler echocardiographic data was obtained at rest and at peak exercise. For each measurement, at least three cardiac cycles were averaged.
Confounders	Variables that demonstrated significance in univariate analyses were included in the multivariate analysis: age ≥65 years, diabetes, rest systolic blood pressure >135 mmHg, LV hypertrophy, rest mean gradient >35 mmHg, increase in mean gradient on exercise >20 mmHg and exercise LV ejection fraction <70%. It is not explicitly stated that these confounders as listed above were included in the MV analysis, but it is suggested based on the discussion in the statistical analysis section of the report. Key confounders in protocol: coronary artery disease and pulmonary disease were exclusion criteria, which covers two of the confounders listed in the protocol. The remaining two (arthritis and peripheral vascular disease) are not mentioned either as exclusion criteria or as confounders adjusted for in the analysis.
Outcomes and effect sizes	**Cardiovascular death or need for aortic valve replacement due to symptoms or LV systolic dysfunction – medically managed – need for valve replacement was part of the outcome** **HR 3.83 (95% CI 2.16 to 6.67) for increase in mean gradient >20 mmHg during exercise vs. increase in mean gradient ≤20 mmHg during exercise** A total of 67 (50%) patients reached end-point during follow-up (58 aortic valve replacements due to development of symptoms, 1 sudden cardiac arrest and underwent replacement, 4 developed severe symptoms but did not have surgery due to severe comorbidities, 1 developed severe symptoms and was waiting for surgery at time of last follow-up, and 3 died from cardiovascular causes).

Reference	Marechaux 2010[160]
	Majority of patients had annual follow-up at centre where baseline exercise stress echocardiogram was performed. Some followed by cardiologists in centres not participating in the study – in these, follow-up was performed by phone interview with patient and treating cardiologist. Mean (SD) follow-up: 20 (14) months. Follow-up was complete in all patients.
Comments, risk of bias and indirectness	Risk of bias: 1. Study participation HIGH 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement HIGH 5. Study confounding HIGH 6. Statistical analysis HIGH 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH Indirectness: • Population – not limited to asymptomatic severe AS but includes some with asymptomatic moderate AS, the proportion of which is unclear. • Confounders – though coronary artery disease and pulmonary disease were exclusion criteria for this study, the other two pre-specified confounders in the protocol are not mentioned as being excluded or adjusted for in the multivariate analysis (downgraded for this in risk of bias so not downgraded further for indirectness)

1

Reference	Peidro 2007[195]
Study type and analysis	Prospective cohort study Cox regression Argentina
Number of participants	N=102 (follow-up complete in these patients, whereas total evaluated was n=106) Symptoms on exercise testing, n=38

Reference	Peidro 2007[195]
and characteristics	No symptoms on exercise testing, n=64 Drop in systolic blood pressure ≥10 mmHg on exercise, n=27 Drop in systolic blood pressure <10 mmHg on exercise, n=75 Downsloping ST segment depression >1 mm on exercise, n=43 (not in the absence of coronary disease as these patients were not excluded) Downsloping ST segment depression ≤1 mm on exercise, n=59 Asymptomatic moderate or severe aortic stenosis – 87% severe. **Inclusion criteria:** Moderate (mean gradient >30 and <50 mmHg) or severe (mean gradient ≥50 mmHg) aortic stenosis; asymptomatic; underwent exercise testing. **Exclusion criteria:** Left ventricular systolic dysfunction on echocardiogram; segmentary abnormalities or left ventricular dysfunction at rest; left bundle branch block; pharmacological treatment with digoxin; artificial pacemaker; ventricular pre-excitation or ST segment depression ≥2 mm on resting ECG; previous coronary events; pulmonary disease; moderate or severe valvular insufficiency. **Values listed below are presented as mean (SD) or number (%)** **Patient characteristics:** • Age: 64.35 (14.41) years • Male sex, 63 (61.8%) • Weight: 75.97 (10.93) kg • Height: 1.67 (0.97) m • Hypertension, 64 (62.7%) • Hypercholesterolaemia, 47 (46.1%) • Diabetes, 11 (10.8%) • History of smoking, 25 (24.5%) • Aortic peak gradient: 83.06 (25.53) mmHg

Reference	Peidro 2007[195]
	• Aortic mean gradient: 50.65 (16.71) mmHg • Aortic valve area: 0.67 (0.17) cm^2 • Severe AS, 87 (85.3%) • Moderate AS, 15 (14.7%) **Exercise testing:** • Abnormal exercise test, 67 (65.7%) • Symptoms on exercise test, 38 (37.3%) • Drop in systolic blood pressure, 27 (26.5%) • Ventricular arrhythmia on exercise test, 38 (37.3%) • Downsloping ST segment depression >1 mm, 43 (42.2%) • Maximum heart rate: 143.6 (24.6) bpm • Maximum systolic blood pressure: 159.7 (25.9) mmHg • Maximum diastolic blood pressure: 84.9 (10.8) mmHg • Maximum functional capacity: 7.9 (3.6) METs **Population source:** Unclear if consecutive. Recruitment period unclear. Single cardiovascular rehabilitation department.
Prognostic variable	Symptoms on exercise testing No symptoms on exercise testing (referent) Drop in systolic blood pressure ≥10 mmHg on exercise Drop in systolic blood pressure <10 mmHg on exercise (referent) Downsloping ST segment depression >1 mm on exercise (not in the absence of coronary disease as these patients were not excluded) Downsloping ST segment depression ≤1 mm on exercise (referent) Exercise testing: Performed on a treadmill using modified Naughton protocol. Performed in especially equipped exercise testing laboratory with continuous 12-lead ECG recording. Blood pressure recorded at last minute of each stage of exercise and at minutes 1, 3 and 5 of recovery. Test was stopped if typical angor (disproportionate to the exercise intensity dyspnoea), a drop in systolic blood pressure ≥10 mmHg, muscular exhaustion or complex ventricular arrhythmias (coupled ventricular beats or ventricular tachycardia)

Reference	Peidro 2007[195]
	occurred. Abnormalities in ST segment was not a reason to stop the stress testing. Patients who presented ST segment depression on resting ECG were considered as abnormal if >1 mm from baseline. The test was considered abnormal if any of the following occurred: presented with angor, syncope or presyncope; dyspnoea or maximal exhaustion to function capacity ≤5 METs in patients younger than 70 years or ≤4 METs in patients older than 70 years; drop in systolic blood pressure ≥10 mmHg with increasing ergometric load; down sloping ST segment depression >1 mm with regard to resting level measured at 80 ms of the J point; and frequent coupled ventricular beats or ventricular tachycardia during exercise or recovery.
Confounders	Unclear which variables were included in the multivariate analysis, but possibly all of those listed in the multivariate analysis table: symptoms on exercise testing, drop in systolic blood pressure and downsloping ST segment depression >1 mm. However, this is very unclear. Key confounders in protocol: pulmonary disease was an exclusion criterion, however the other three confounders listed in the protocol not excluded or mentioned in terms of multivariate analysis.
Outcomes and effect sizes	**Cardiovascular death or aortic valve replacement – medically managed as surgery captured as part of the outcome** **OR 2.48 (95% CI 1.32 to 4.67) for symptoms vs. no symptoms on exercise testing** **OR 1.95 (95% CI 1.00 to 3.82) for drop in systolic blood pressure ≥10 mmHg vs. <10 mmHg on exercise testing** **OR 1.89 (95% CI 1.03 to 3.48) for downsloping ST segment depression >1 mm vs. ≤1 mm on exercise testing** Aortic valve replacements were indicated in 45 patients and there were 2 deaths. Follow-up conducted by reviewing clinical records and personal or telephone interviews with patients and general practitioners. Median (IQR) follow-up: 10.7 (4.9-19.4) months.
Comments, risk of bias and indirectness	Risk of bias: For symptoms on exercise prognostic factor 1. Study participation HIGH 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement HIGH 5. Study confounding HIGH 6. Statistical analysis HIGH

Reference	Peidro 2007[195]
	7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH <u>For drop in systolic blood pressure on exercise prognostic factor</u> 1. Study participation HIGH 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement HIGH 5. Study confounding HIGH 6. Statistical analysis HIGH 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH <u>For ST segment depression on exercise prognostic factor</u> 1. Study participation HIGH 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement HIGH 5. Study confounding HIGH 6. Statistical analysis HIGH 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH Indirectness: <u>For symptoms on exercise prognostic factor</u> • Population– not limited to asymptomatic severe AS as includes some with asymptomatic moderate AS – 87% of the population have severe AS. • Confounders – though pulmonary disease is an exclusion criterion, other three confounders listed in the protocol are not mentioned as exclusion criteria or adjusted for in the multivariate analysis (downgraded for this in risk of bias so not downgraded further for indirectness). <u>For drop in systolic blood pressure on exercise prognostic factor</u>

Reference	Peidro 2007[195]
	• Population– not limited to asymptomatic severe AS as includes some with asymptomatic moderate AS – 87% of the population have severe AS. • Prognostic factor – threshold used in study differs to that specified in protocol, as ≥10 mmHg drop in systolic blood pressure on exercise is used rather than ≥20 mmHg drop on exercise. • Confounders – though pulmonary disease is an exclusion criterion, other three confounders listed in the protocol are not mentioned as exclusion criteria or adjusted for in the multivariate analysis (downgraded for this in risk of bias so not downgraded further for indirectness). <u>For ST segment depression on exercise prognostic factor</u> • Population– not limited to asymptomatic severe AS as includes some with asymptomatic moderate AS – 87% of the population have severe AS. • Prognostic factor – threshold used in study differs to that specified in protocol, as >1 mmHg ST segment depression on exercise is used rather than >2 mm ST segment depression on exercise. Coronary disease is also not absent in all patients, which was specified in the protocol as important when interpreting this prognostic factor. The study states that ST segment depression >1 mm did not identify those patients with associated coronary disease. • Confounders – though pulmonary disease is an exclusion criterion, other three confounders listed in the protocol are not mentioned as exclusion criteria or adjusted for in the multivariate analysis (downgraded for this in risk of bias so not downgraded further for indirectness).

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Reference	Singh 2013[230] and Singh 2017[231]
Study type and analysis	Prospective cohort study PRIMID-AS Cox proportional hazards regression UK
Number of participants and characteristics	N=123 (for the severe subgroup only, the whole cohort total was n=174) Positive exercise test (symptom development as defined in study), n=not reported for the severe subgroup Negative exercise test, n=not reported for the severe subgroup

Reference	Singh 2013[230] and Singh 2017[231]
	Severe asymptomatic AS – study includes moderate or severe asymptomatic AS but provided results for the severe subgroup separately in supplementary material. **Inclusion criteria:** Aged 18-85 years; moderate to severe aortic stenosis (≥2 of aortic valve area <1.5 cm^2, peak pressure gradient >36 mmHg and mean pressure gradient >25 mmHg); asymptomatic; and ability to perform bicycle exercise test. **Exclusion criteria:** Absolute contraindications to cardiovascular magnetic resonance; adenosine (severe asthma) or contrast administration (severe renal disease); previous cardiac surgery; LV ejection fraction <40%; persistent atrial fibrillation/flutter; other severe valve disease; previous heart failure; planned aortic valve replacement; and comorbidity limiting life expectancy or precluding aortic valve replacement. **Values listed below are presented as mean (SD) or number (%):** note – the details below are for the whole cohort (moderate or severe AS), as details for the severe subgroup have not been provided separately **Patient characteristics:** • Age: 66.2 (13.34) years • Male sex, 133 (76.4%) • Body surface area: 2.0 (0.21) m^2 • Resting heart rate: 70.3 (11.43) bpm • Resting systolic blood pressure: 146.9 (21.09) mmHg • Resting diastolic blood pressure: 77.2 (10.65) mmHg • Diabetes, 25 (14.4%) • Hypertension, 93 (53.4%) • Hyperlipidaemia, 92 (52.9%) • ACE-inhibitors/ARBs, 77 (44.3%) • Beta-blocker, 54 (31%) • Statin, 105 (60.3%) • NT-proBNP, median (IQR): 56.51 (19.22; 152.52) • Haemoglobin: 14.2 (1.24) g/dl • eGFR: 88 (28.6) ml/min

Reference	Singh 2013[230] and Singh 2017[231]
	• Peak aortic jet velocity: 3.86 (0.56) m/s • Mean pressure gradient: 35.4 (12.49) mmHg • Aortic valve area indexed: 0.57 (0.14) cm^2/m^2 • E/A: 0.88 (0.29) • Septal E/e': 12.28 (4.86) • Lateral E/e': 9.88 (3.72) • Valvulo-arterial impedance: 3.96 (1.06) mmHg/ml/m^2 • LV end-diastolic volume index: 87.58 (18.31) ml/m^2 • LV end-systolic volume index: 38.28 (10.68) ml/m^2 • LV stroke volume: 97.11 (23.25) ml • LV stroke volume index: 49.30 (9.34) ml/m^2 • LV ejection fraction: 56.70 (4.96)% • LV mass/volume: 0.67 (0.11) g/m^2 • Left atrial volume index: 54.93 (30.44) ml/m^2 **Exercise testing:** note – the details below are for the whole cohort (moderate or severe AS), as details for the severe subgroup have not been provided separately • Exercise duration: 8.49 (2.02) min • Peak workload: 109.9 (40.2) W • % predicted workload: 86.35 (27.53)% • % predicted heart rate: 86.74 (11.83)% • Rise in systolic blood pressure: 41.38 (22.25) mmHg • Positive exercise test (strict definition), 19 (10.9%) • Positive exercise test (conventional definition), 55 (31.6%) **Population source:** Conducted in 10 hospitals across the UK between April 2012 and November 2014. Unclear if consecutive included.
Prognostic variable	Positive exercise test (symptom development as defined in study) Negative exercise test (referent)

Reference	Singh 2013[230] and Singh 2017[231]
	Exercise testing: Incremental symptom-limited exercise tolerance test performed on stationary bicycle. Exercise test was considered to be 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). As guidelines consider symptoms at any stage indicative of symptoms, this conventional definition of a symptomatically positive test was also considered. In patients who stopped due to fatigue, exercise test was considered negative or inconclusive if ≥80% or <80% of the predicted workload was achieved, respectively.
Confounders	Variables that were included in the multivariate analysis: sex, NT-proBNP, aortic valve area index, cardiac magnetic resonance LV mass/volume ratio, myocardial perfusion reserve and positive exercise tolerance test (strict definition). Multivariate models were built using stepwise selection approach. Key confounders in protocol: none of the confounders specified in the protocol were included in the multivariate analysis and were not mentioned as exclusion criteria.
Outcomes and effect sizes	**Cardiovascular death, typical AS symptoms indicating aortic valve replacement referral or major adverse cardiac events (hospitalisation for heart failure, chest pain, syncope or arrhythmia) – medically managed initially as indication for aortic valve replacement captured as part of the outcome** **HR 2.94 (95% 1.29 CI to 6.70) for positive (symptom development) vs. negative exercise tolerance test – (strict definition defined in the study)** Note: Exercise test was considered to be 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 A total of 41 patients in the severe subgroup experienced events during follow-up. Patients were seen or contacted by phone every 6 months for at least 12 months or until a pre-defined endpoint occurred, or for a maximum of 30 months. Median (IQR) follow-up: 374 (351-498) days – for the whole cohort, not limited to the severe subgroup
Comments, risk of bias and indirectness	Risk of bias: 1. Study participation HIGH 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement HIGH 5. Study confounding HIGH 6. Statistical analysis HIGH

Reference	Singh 2013[230] and Singh 2017[231]	
	7. Other risk of bias	LOW
	OVERALL RISK OF BIAS	VERY HIGH
	Indirectness: • Confounders – have not adjusted for any of the pre-specified confounders listed in the protocol or mentioned them as exclusion criteria so these factors may be contributing to the results (downgraded for this in risk of bias so not downgraded further for indirectness)	

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D2 Symptomatic low-flow aortic stenosis

Reference	Annabi 2018[9]
Study type and analysis	Prospective multicentre cohort study TOPAS study Cox proportional hazards regression model Canada, Austria, Germany, USA
Number of participants and characteristics	N=88 (results only given for medical management arm, total study n=186) Mean aortic gradient ≥40 mmHg at peak stress (severe status unmasked in response to stress), n= not reported Mean aortic gradient <40 mmHg at peak stress, n= not reported Study states that patients with mean aortic gradient ≥40 mmHg at peak stress were underrepresented in the medical management group as they were more likely to undergo surgery. Low-flow low-gradient aortic stenosis. At least 40% symptomatic as NYHA class III or IV, but unclear whether remaining proportion symptomatic. **Inclusion criteria:** Mean aortic gradient <40 mmHg, indexed aortic valve area ≤0.6 cm^2 and LVEF ≤40% on resting echocardiogram.

Reference	Annabi 2018[9]
	Exclusion criteria: More than mild aortic regurgitation, moderate mitral regurgitation or mild stenosis assessed according to existing guidelines. **Values listed below are presented as mean (SD) or number (%)** **Patient characteristics:** • Age: 73 (10) years • Male/female: 69/19 (78%/22%) • Diabetes, 35% • Kidney failure, 28% • Hypertension, 68% • Hyperlipidaemia, 64% • Chronic obstructive pulmonary disease, 24% • Coronary artery disease, 76% • Previous myocardial infarction, 64% • Duke activity status index: 24 (16) • NYHA functional class ≥III, 40% • Atrial fibrillation/flutter, 8% • LV diameter, 62 (10) mm • Mean gradient, 20 (8) mmHg • Aortic valve area, 0.94 (0.25) cm^2 • Stroke volume, 58 (18) ml • Transvalvular flow rate, 189 (55) ml/sec • LV ejection fraction, 28 (9)% • LV flow reserve, 45% • Increase in Q_{mean} ≥15%, 90% **Dobutamine stress testing:** values at peak stress • Mean gradient, 27 (10) mmHg • Aortic valve area, 1.11 (0.28) cm^2

Reference	Annabi 2018[9]
	• Stroke volume, 68 (20) ml • Transvalvular flow rate, 274 (84) ml/sec • LV ejection fraction, 35 (11)% • Projected aortic valve area, 1.09 (0.23) cm^2 **Population source:** Multicentre study part of the TOPAS study. Likely to be consecutive matching inclusion criteria but not explicitly stated.
Prognostic variable	Mean aortic gradient ≥40 mmHg at peak stress (severe status unmasked in response to stress) Mean aortic gradient <40 mmHg at peak stress (referent) Dobutamine stress testing: dobutamine infusion consisted of 8 min stages with increments of 2.5-5.0 µg/kg/min up to a max. does of 20 µg/kg/min. Peak stress values were obtained when mean gradient was maximal during stress testing, which was not necessarily during the last stage with maximum dose of dobutamine.
Confounders	Cox proportional hazard models were adjusted for age, sex, functional capacity (Duke activity status index), kidney failure and LVEF at peak dobutamine stress in patients that received medical management. Key confounders in protocol: not adjusted for any of the four confounders listed in the protocol and none mentioned in the exclusion criteria.
Outcomes and effect sizes	**Mortality at 4 years – those undergoing medical management** **HR 0.93 (95% CI 0.21 to 4.07) for mean aortic gradient ≥40 mmHg vs. <40 mmHg at peak stress (increase in mean gradient to severe range vs. no increase in mean gradient to severe range)** Note: elsewhere in the study a different HR and CI range were given for this outcome adjusted for the same confounders in the same population – as the value reported above was reported on two separate occasions in the study, this has been used and the other assumed to be an error. Patients were followed annually for 5 years. Range or mean follow-up duration not reported.
Comments, risk of bias and indirectness	Risk of bias: 1. Study participation HIGH 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement LOW

Reference	Annabi 2018[9]	
	5. Study confounding	HIGH
	6. Statistical analysis	HIGH
	7. Other risk of bias	LOW
	OVERALL RISK OF BIAS	VERY HIGH
	Indirectness: • Population – unclear if 60% not in NYHA class III or IV also had symptoms, so may not represent a symptomatic low-flow AS population specified in the protocol as may include some asymptomatic low-flow patients. • Confounding factors – none of the key confounders listed in protocol were excluded or adjusted for in multivariate analysis so may have differed between the prognostic factor groups (downgraded for this in risk of bias so not downgraded further for indirectness)	

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Reference	Fougeres 2012[72]
Study type and analysis	Prospective cohort study Cox proportional hazards regression France, Belgium
Number of participants and characteristics	N=107 No increase in aortic valve area to >1.2 cm^2 on dobutamine echocardiography testing (true severe AS with contractile reserve or those with no contractile reserve), n=78 Increase in aortic valve area to >1.2 cm^2 on dobutamine echocardiography testing (pseudo-severe AS with contractile reserve), n=29 Symptomatic low-flow aortic stenosis (severe based on valve area prior to dobutamine testing) **Inclusion criteria:** Presence of severe symptomatic aortic stenosis (severe based on aortic valve area ≤1 cm^2 or indexed aortic valve area ≤0.6 cm^2/m^2); low pressure gradient (mean transaortic pressure gradient <40 mmHg); low left ventricular ejection fraction (≤40%); and low cardiac index (≤3.0 $L/min/m^2$). **Exclusion criteria:**

Reference	Fougeres 2012[72]

	Severe extra-cardiac comorbidities (life expectancy <1 year); more than mild aortic or mitral regurgitation; and atrial fibrillation.
	
	Values listed below are presented as median (IQR) or number (%)
	
	Patient characteristics:
	<u>Whole cohort</u>
	• Age: 76 (69-81) years
	• Male sex: 78%
	• Severe symptoms reported in all patients, including class III-IV symptoms of:
	  ○ Dyspnoea, 79%
	  ○ Angina pectoris, 10%
	  ○ Syncope, 2%
	
	<u>Pseudo-severe AS (with contractile reserve and increase in aortic valve area to >1.2 cm^2 on dobutamine testing) – n=29</u>
	• NYHA class II/III/IV, 24%/55%/21%
	• Hypertension, 31%
	• Diabetes mellitus, 28%
	• Coronary artery disease, 62%
	• Multivessel coronary artery disease, 41%
	• Prior myocardial infarction, 31%
	• Diastolic septal thickness: 12 (11-14) mm
	• Left ventricular end-diastolic diameter: 65 (60-69) mm
	• LV ejection fraction: 30 (20-39)%
	• Cardiac index: 2.2 (1.9-2.6) l/min/m^2
	• Stroke volume: 58 (46-64) ml
	• Dobutamine increase in stroke volume: 46 (18-52) ml
	• Baseline aortic valve area: 1.0 (0.85-1.05) cm^2
	• Dobutamine aortic valve area: 1.3 (1.2-1.4) cm^2
	• Dobutamine increase in aortic valve area: 0.3 (0.2-0.4) cm^2
	• Baseline indexed aortic valve area: 0.5 (0.4-0.6) cm^2/m^2

Reference	Fougeres 2012[72]
	• Baseline mean pressure gradient: 18 (13-23) mmHg • Dobutamine mean pressure gradient: 25 (20-31) mmHg • Baseline mean pressure gradient ≤20 mmHg, 55% • Dobutamine peak dose: 10 (9-14) µg/kg/min • Systolic pulmonary artery pressure: 51 (41-61) mmHg • Logistic EuroSCORE: 14 (6-26)% <u>True-severe AS (with contractile reserve and no increase in aortic valve area to >1.2 cm^2 on dobutamine testing) – n=43</u> • NYHA class II/III/IV, 14%/60%/26% • Hypertension, 26% • Diabetes mellitus, 23% • Coronary artery disease, 56% • Multivessel coronary artery disease, 30% • Prior myocardial infarction, 19% • Diastolic septal thickness: 12 (11-14) mm • Left ventricular end-diastolic diameter: 62 (53-69) mm • LV ejection fraction: 32 (23-35)% • Cardiac index: 1.9 (1.5-2.4) l/min/m^2 • Stroke volume: 44 (35-54) ml • Dobutamine increase in stroke volume: 35 (30-48) ml • Baseline aortic valve area: 0.7 (0.6-0.8) cm^2 • Dobutamine aortic valve area: 0.9 (0.7-1.0) cm^2 • Dobutamine increase in aortic valve area: 0.1 (0.1-0.2) cm^2 • Baseline indexed aortic valve area: 0.4 (0.4-0.5) cm^2/m^2 • Baseline mean pressure gradient: 24 (18-29) mmHg • Dobutamine mean pressure gradient: 34 (28-43) mmHg • Baseline mean pressure gradient ≤20 mmHg, 37% • Dobutamine peak dose: 12 (10-15) µg/kg/min • Systolic pulmonary artery pressure: 50 (44-60) mmHg • Logistic EuroSCORE: 14 (7-27)%

Reference	Fougeres 2012[72]
	<u>No contractile reserve (no contractile reserve on dobutamine testing and whether true/pseudo-severe AS could not be determined) – n=35</u> • NYHA class II/III/IV, 24%/56%/20% • Hypertension, 23% • Diabetes mellitus, 17% • Coronary artery disease, 66% • Multivessel coronary artery disease, 43% • Prior myocardial infarction, 26% • Diastolic septal thickness: 11 (9-13) mm • Left ventricular end-diastolic diameter: 60 (53-67) mm • LV ejection fraction: 27 (25-30)% • Cardiac index: 2.2 (1.8-2.4) l/min/m^2 • Stroke volume: 47 (35-59) ml • Dobutamine increase in stroke volume: 11 (5-17) ml • Baseline aortic valve area: 0.7 (0.6-0.9) cm^2 • Dobutamine aortic valve area: 0.8 (0.6-1.0) cm^2 • Dobutamine increase in aortic valve area: 0.0 (0.0-0.1) cm^2 • Baseline indexed aortic valve area: 0.4 (0.3-0.5) cm^2/m^2 • Baseline mean pressure gradient: 22 (18-27) mmHg • Dobutamine mean pressure gradient: 29 (24-39) mmHg • Baseline mean pressure gradient ≤20 mmHg, 40% • Dobutamine peak dose: 10 (10-15) µg/kg/min • Systolic pulmonary artery pressure: 53 (41-61) mmHg • Logistic EuroSCORE: 15 (11-26)% **Population source:** European multicentre registry of low-flow low-gradient aortic stenosis (LF/LGAS) between October 1993 and February 2010 – 8 medical centres in France and Belgium. Likely to be consecutive matching criteria but unclear.
Prognostic variable	No increase in aortic valve area to >1.2 cm^2 on dobutamine echocardiography testing (true severe AS with contractile reserve or those with no contractile reserve)

Reference	Fougeres 2012[72]
	Increase in aortic valve area to >1.2 cm^2 on dobutamine echocardiography testing (pseudo-severe AS with contractile reserve; referent) Left ventricular contractile reserve was defined by an increase in the stroke volume of ≥20% under dobutamine testing relative to baseline. In those with demonstrated contractile reserve, they were further divided into pseudo-severe or true-severe AS based on valve area. Pseudo-severe aortic stenosis was defined by a final aortic valve area ≥1.2 cm^2 with a mean pressure gradient <40 mmHg at peak dobutamine infusion. Pseudo/true-severe AS could not be differentiated in those with no contractile reserve on dobutamine testing.
Confounders	Established risk factors for aortic stenosis and baseline variables that were significantly different (P<0.05) between groups were included in the multivariate analysis: pseudo AS vs. other groups, logistic EuroSCORE, baseline mean pressure gradient and male sex. Key confounders in protocol: none of those matching protocol were included in the multivariate analysis. Only life-limiting extra-cardiac conditions (<1-year life expectancy) were excluded from the study so possibly some with lung disease/respiratory insufficiency but not reported. Similarly, peripheral vascular disease and arthritis not mentioned, and coronary artery disease reported to be different between those that died and survived.
Outcomes and effect sizes	**Overall mortality – patients that were conservatively managed for >6 months** **HR 1.89 (95% CI 1.33 to 2.70) for no increase in aortic valve area to >1.2 cm^2 (true severe AS or no contractile reserve) vs. increase in aortic valve area to >1.2 cm^2 (pseudo-severe AS) on dobutamine testing** Note: the HR in the study was reported with no increase in valve area on stress testing or a lack of contractile reserve as the referent. To better match the protocol this has been inverted to report increase in valve area on stress testing (pseudo-severe AS) as the referent. Note, in the no contractile reserve group, valve areas appear to increase very little on dobutamine testing as reported in the patient characteristics table, similar to the true-severe AS group with contractile reserve and may therefore also not have demonstrated an increase on dobutamine testing though this is not explicitly reported. At latest follow-up, 74 (69%) of patients had died (median interval of 10 months, range 4-21 months). 81% of all deaths were from cardiac causes. Causes of death: congestive heart failure (n=45), sudden death (n=15), pulmonary disease (n=4), cancer (n=2), stroke (n=1), renal failure (n=1) or unknown cause (n=6). Median (range) follow-up: 25 (7-54) months.

Reference	Fougeres 2012[72]
Comments, risk of bias and indirectness	Risk of bias: 1. Study participation LOW 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement LOW 5. Study confounding HIGH 6. Statistical analysis LOW 7. Other risk of bias LOW OVERALL RISK OF BIAS HIGH Indirectness: • Prognostic factor – in the subgroup with no contractile reserve it was not possible to determine whether it was true-severe AS or pseudo-severe AS based on increase/no increase in valve area and the study reports them as a separate, third group. However, for the multivariate analysis the no contractile reserve subgroup is combined with true-severe AS and it is unclear whether this group experienced an increase in valve area or not. Based on study characteristics table, only small increases in valve area reported in the no contractile reserve group so may all have shown no increase as well as in the true-severe AS group, though this is unclear. • Confounders – have not adjusted for any of the pre-specified confounders listed in the protocol or mentioned them as exclusion criteria so these factors may be contributing to the results (downgraded for this in risk of bias so not downgraded further for indirectness)

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Reference	Plonska-Gosciniak 2013[204]
Study type and analysis	Prospective cohort study Cox proportional hazards regression Poland, Belgium
Number of participants and characteristics	N=39 No increase in aortic valve area during stress testing, n= unclear Increase in aortic valve area during stress testing, n= unclear

Reference	Plonska-Gosciniak 2013[204]
	Symptomatic low-flow AS – small proportion appear to be asymptomatic low-flow AS (12.8% in NYHA class I) **Inclusion criteria:** Aortic stenosis (peak gradient >25 mmHg); depressed LV systolic dysfunction (LV ejection fraction ≤45%); and low transaortic pressure gradient (peak gradient ≤45 mmHg and mean gradient ≤35 mmHg). **Exclusion criteria:** Chronic atrial fibrillation; other significant valve disease; moderate or severe aortic regurgitation; contraindications to low-dose dobutamine stress echocardiography; clinical and haemodynamic instability; implanted pacemaker; and poor quality of echocardiography images at rest precluding assessment of LV contractility, valve morphology and function. **Values listed below are presented as mean (SD) or number (%)** **Patient characteristics:** • Age: 59 (13) years • Male sex, 34 (87.2%) • Weight: 77 (11) kg • Height: 172 (7) cm • Body mass index: 26 (3) kg/m^2 • Body surface area: 1.90 (0.15) m^2 • Dyslipidaemia, 18 (46.2%) • Diabetes, 4 (10.3%) • Hypertension, 16 (41.0%) • Smoking history, 13 (33.3%) • Previous myocardial infarction, 4 (10.3%) • Dyspnoea at rest, 10 (25.6%) • Peripheral oedema, 4 (10.3%) • Fatigue, 25 (64.1%) • History of angina, 14 (35.9%) • Ventricular arrhythmia, 4 (10.3%) • Dyspnoea at exertion, 25 (64.1%)

Reference	Plonska-Gosciniak 2013[204]

	• Atypical chest pain, 8 (20.5%)
	• Syncope, 7 (17.9%)
	• Vertigo, 1 (2.6%)
	• Significant coronary artery disease (≥50% stenosis), 21 (53.8%)
	  ○ Single vessel, 7 (18%)
	  ○ Two-vessel, 7 (18%)
	  ○ Three-vessel, 7 (18%)
	• NYHA class:
	  ○ I, 5 (12.8%)
	  ○ II, 18 (46.2%)
	  ○ III, 16 (41.0%)
	• Heart rate: 76 (12) bpm
	• Systolic blood pressure: 136 (24) mmHg
	• Diastolic blood pressure: 84 (11) mmHg
	• LV ejection fraction: 39 (8)%
	• Aortic valve area: 0.8 (0.2) cm^2
	• Mean aortic gradient: 24.0 (5.5) mmHg
	• Peak aortic gradient: 37.5 (6.4) mmHg
	• Aortic Vmax: 3.11 (0.4) m/s
	
	Dobutamine stress testing:
	• Heart rate: 82 (12) bpm
	• Systolic blood pressure: 137 (19) mmHg
	• Diastolic blood pressure: 84 (11) mmHg
	• LV ejection fraction: 45.3 (10)%
	• Aortic valve area: 0.99 (0.29) cm^2
	• Mean aortic gradient: 31.8 (8.5) mmHg
	• Peak aortic gradient: 52 (14.2) mmHg
	• Aortic Vmax: 3.57 (0.49) m/s
	• Preserved contractile reserve, 27 (69.2%)

Reference	Plonska-Gosciniak 2013[204]
	• No contractile reserve, 12 (30.8%) • Of those with contractile reserve preserved, true-severe AS diagnosed in 12 patients and pseudo-severe AS in 15 patients. **Population source:** Multicentre prospective study at various centres in Belgium and Poland. Unclear time-period patients were recruited between. Unclear if consecutive.
Prognostic variable	No increase in aortic valve area during stress testing Increase in aortic valve area during stress testing (referent) Based on difference between peak and baseline ejection fraction, patients were classified as having preserved contractile reserve (≥20% increase in LV ejection fraction on stress testing) or as having no contractile reserve (<20% increase in LV ejection fraction on stress testing). In those with preserved contractile reserve, patients with an aortic valve area increase during stress testing ≤0.3 cm^2 were classified as having true-severe AS, while patients with >0.3 cm^2 increase in aortic valve area during stress testing, or an aortic valve area >1 cm^2 at peak dose of dobutamine, were classed as having pseudo-severe AS. Dobutamine stress testing: All underwent low-dose dobutamine stress echocardiography. Abstained from beta-blockers and calcium antagonists for at least 24 h prior to the test. All other medications were continued as prescribed. Dobutamine sequence was 5 µg/kg/min and 10 µg/kg/min, each of which was maintained for 3 min with an infusion pump. Echocardiography images acquired at each stage of the testing. Transaortic peak and mean gradients were measured at each stage and aortic valve area was determined. LV wall motion was assessed visually, and LV ejection fraction was measured at each stage.
Confounders	Variables that demonstrated significance (P<0.1) on univariate analyses were included in the multivariate analysis: unclear which confounders included in the multivariate analysis, but may include aortic valve area at peak stress, absence of aortic valve area increase during stress, absence of contractile reserve and presence of significant coronary artery disease. May however have included more than this. Key confounders in protocol: unclear which confounders have been adjusted for in the analysis – may however have included coronary artery disease but none of the others pre-specified in the protocol are mentioned as exclusion criteria or possible confounders adjusted for.
Outcomes and effect sizes	**Death, myocardial infarction or significant worsening of heart failure symptoms (pulmonary oedema) – medically and surgically treated patients combined and not adjusted for in analysis** **HR 5.7 (95% CI 2.0 to 16.0) for absence vs. presence of increase in aortic valve area during stress testing**

Reference	Plonska-Gosciniak 2013[204]
	Note: it is reported to be presented as an OR in the study, but they state that Cox proportional hazards regression was performed for multivariate analysis. Therefore, the results have been extracted as a HR. Note has not been adjusted for whether they received medical or surgical treatment so may affect the results. During follow-up, 4 deaths, 3 myocardial infarctions and 3 cases of pulmonary oedema occurred. Mean (SD) follow-up: 353 (38) days.
Comments, risk of bias and indirectness	Risk of bias: 1. Study participation — HIGH 2. Study attrition — LOW 3. Prognostic factor measurement — LOW 4. Outcome Measurement — HIGH 5. Study confounding — HIGH 6. Statistical analysis — HIGH 7. Other risk of bias — LOW OVERALL RISK OF BIAS — VERY HIGH Indirectness: • Population – not limited to symptomatic low-flow AS as appears to include some that are asymptomatic (NYHA class I) – 87% are symptomatic low-flow AS • Confounders – though one of the pre-specified confounders may have been adjusted for, this is unclear and may not have been, and the other three listed in the protocol are not mentioned as exclusion criteria or as potential confounders adjusted for in the analysis (downgraded for this in risk of bias so not downgraded further for indirectness). • Outcomes – combines medically and surgically treated patients in the same analysis and has not included this as a confounding factor, whereas in the protocol ideally separate results for those medically and surgically treated could be extracted

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D.3 Asymptomatic severe mitral regurgitation

Reference	Magne 2010[155]
Study type and analysis	Prospective cohort study Cox proportional hazards model Belgium
Number of participants and characteristics	N=78 Exercise pulmonary hypertension (SPAP >60 mmHg), n=36 No exercise pulmonary hypertension (SPAP ≤60 mmHg), n=42 Asymptomatic moderate or severe degenerative mitral regurgitation – 60% severe MR **Inclusion criteria:** Asymptomatic; degenerative mitral regurgitation; preserved left ventricular systolic function (LV end-systolic diameter <45 mm and LV ejection fraction >60%); at least moderate mitral regurgitation (effective regurgitant orifice area >20 mm^2 or regurgitant volume >30 ml); referred for exercise stress echocardiography. **Exclusion criteria:** Concomitant valvular stenosis or regurgitation; atrial arrhythmias; inability to exercise; stress-induced myocardial ischaemia; and absence of measurable systolic pulmonary artery pressure during exercise. **Values listed below are presented as mean (SD) or number (%)** **Patient characteristics:** • Age: 61 (13) years • Male sex: 44 (56%) • Severe MR, 47 (60%) • Resting pulmonary hypertension (SPAP >50 mmHg), 12 (15%) • Body mass index: 26 (4) kg/m^2 • Heart rate: 73 (11) bpm • Systolic arterial pressure: 138 (18) mmHg

Reference	Magne 2010[155]

	• Diastolic arterial pressure: 78 (12) mmHg
	• Hypertension, 43 (55%)
	• Hypercholesterolaemia, 16 (20%)
	• Diabetes mellitus, 8 (10%)
	• Smoker, 27 (35%)
	• Medication
	  ○ ACE inhibitor, 34 (44%)
	  ○ Beta-blockers, 34 (44%)
	  ○ Diuretics, 2 (3%)
	• Mitral valve prolapse
	  ○ Anterior, 5 (7%)
	  ○ Posterior, 37 (47%)
	  ○ Both, 36 (46%)
	  ○ Mitral flail, 8 (10%)
	• Resting effective regurgitant orifice: 43 (20) mm^2
	• Resting regurgitant volume: 71 (27) ml
	• Resting systolic pulmonary artery pressure (SPAP): 39 (11) mmHg
	• LV end-systolic volume: 36 (11) ml
	• LV end-diastolic volume: 114 (35) ml
	• Resting left atrial volume: 71 (24) ml
	• LV ejection fraction: 69 (6)%
	• E-wave velocity: 100 (33) cm/s^{-1}
	• A-wave velocity: 75 (25) cm/s^{-1}
	• E/A ratio: 1.5 (0.7)
	• Ea-wave velocity: 7.4 (1.9) cm/s
	• E/Ea ratio: 14 (5)
	
	Exercise testing:
	• Exercise SPAP: 62 (17) mmHg
	• Exercise pulmonary hypertension (SPAP >60 mmHg), 36 (46%)

Reference	Magne 2010[155]
	• Exercise effective regurgitant orifice: 48 (26) mm^2 • Exercise regurgitant volume: 73 (36) ml • LV end-systolic volume: 31 (16) ml • LV end-diastolic volume: 106 (39) ml • Exercise left atrial volume: 81 (29) ml • LV ejection fraction: 72 (9)% • E-wave velocity: 138 (42) cm/s^{-1} • A-wave velocity: 94 (43) cm/s^{-1} • E/A ratio: 1.5 (0.4) • Ea-wave velocity: 9.9 (2.3) cm/s • E/Ea ratio: 14.5 (5) **Population source:** Consecutive patients matching inclusion criteria between September 2005 and September 2009 at university hospital in Belgium.
Prognostic variable	Exercise pulmonary hypertension (SPAP >60 mmHg) No exercise pulmonary hypertension (SPAP ≤60 mmHg; referent) Exercise echocardiography: Symptom-limited graded bicycle exercise test performed in semi-supine position on dedicated tilting exercise table. Initial workload of 25 W maintained for 2 min and workload was increased by 25 W every 2 min. Blood pressure and a 12-lead ECG were recorded every 2 min. 2D and Doppler echocardiographic imaging was available throughout the test.
Confounders	Variables that demonstrated significance (P<0.10) in univariate analysis were included in the multivariate analysis: age, sex, resting E-wave velocity, exercise left ventricular end-diastolic volume and exercise pulmonary hypertension (SPAP >60 mmHg) Key confounders in protocol: none of those listed in protocol included as confounders in the MV analysis or excluded from the study. None mentioned in study characteristics tables either.
Outcomes and effect sizes	**Development of symptoms – medically managed – not explicitly stated but those operated on were only operated on following development of symptoms which is therefore captured in the outcome** **HR 2.1 (95% CI 1.4 to 3.1) for exercise pulmonary hypertension (SPAP >60 mmHg) vs. no exercise pulmonary hypertension (SPAP ≤60 mmHg** Note: various models reported but the one that adjusted for most confounders was extracted

Reference	Magne 2010[155]
	During follow-up, 51% remained asymptomatic and 49% developed symptoms. Symptom-free survival was 71±5% and 54±6% at 1 and 2 years, respectively. A total of 5 patients were hospitalised for congestive heart failure, 1 for syncope and 1 for acute pulmonary oedema. 4 patients developed atrial fibrillation. The mitral valve was operated on in 25 patients (5 valve replacements and 20 valve repairs). All operations were performed due to symptoms. No operative mortality was observed but 5 patients died postoperatively. Patients were classified as symptomatic when shortness of breath, angina, dizziness or syncope with exertion was identified during follow-up. Physical examination and echocardiography were performed by experienced cardiologists and symptomatic status was carefully assessed. Patients were evaluated every 12 months, including physical examination and echocardiography. Intervals were shorted to 6 or 3 months in patients with changes relative to previous measurements or if echocardiographic measurements were close to guideline cut-off values used for surgical indication. At the end of the study, those with a last follow-up at >6 months were re-evaluated with telephone calls from physicians. To ensure blinding, data on exercise-induced changes in MR severity and systolic pulmonary artery pressure were not sent to the referral physician. Exercise pulmonary hypertension was defined as systolic pulmonary artery pressure >60 mmHg. It was derived from the regurgitant jet of tricuspid regurgitation using systolic transtricuspid pressure gradient calculated by modified Bernoulli equation. Range of follow-up: 2-56 months. Mean (SD) follow-up: 19 (14) months.
Comments, risk of bias and indirectness	Risk of bias: 1. Study participation — HIGH 2. Study attrition — LOW 3. Prognostic factor measurement — LOW 4. Outcome Measurement — LOW 5. Study confounding — HIGH 6. Statistical analysis — HIGH 7. Other risk of bias — LOW OVERALL RISK OF BIAS — VERY HIGH Indirectness: • Population – not limited to asymptomatic severe MR but includes some with asymptomatic moderate MR. 60% reported to be asymptomatic severe MR. • Confounders – have not adjusted for any of the pre-specified confounders listed in the protocol or mentioned them as exclusion criteria so these factors may be contributing to the results (downgraded for this in risk of bias so not downgraded further for indirectness)

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Reference	Magne 2014[157]
Study type and analysis	Prospective cohort study Cox proportional hazards regression model Belgium, Canada
Number of participants and characteristics	N=115 Absence of contractile reserve (exercise-induced improvement in global longitudinal strain <2%), n=57 Presence of contractile reserve (exercise-induced improvement in global longitudinal strain ≥2%), n=58 Asymptomatic moderate or severe primary mitral regurgitation – 63% severe **Inclusion criteria:** Asymptomatic; moderate to severe degenerative mitral regurgitation (effective regurgitant orifice area ≥20 mm^2 and/or regurgitant volume ≥30 ml); preserved LV ejection fraction (>60%); normal LV end-systolic diameter (<45 mm); referred to outpatient valve disease clinic for exercise Doppler echocardiography; in sinus rhythm; and had LV contractile reserve assessment available by both global longitudinal strain and LV ejection fraction **Exclusion criteria:** Concomitant >mild valvular stenosis or regurgitation; renal failure; suspected coronary arterial disease; electrical changes during exercise; and exercise-induced wall motion abnormalities. **Values listed below are presented as mean (SD) or number (%)** **Patient characteristics:** • Age: 61 (14) years • Male sex, 64 (56%) • Severe MR, 73 (63%) • Hypertension, 54 (47%) • Overweight, 53 (46%) • Hypercholesterolaemia, 25 (22%) • Diabetes, 9 (8%)

Reference	Magne 2014[157]
	• History of smoking, 40 (35%) • Body surface area: 1.86 (0.2) m^2 • Heart rate: 71.02 (11.68) bpm • Systolic blood pressure: 139.50 (19.88) mmHg • Diastolic blood pressure: 76.49 (12.09) mmHg • LV end-systolic diameter: 33.99 (6.08) mm • LV end-diastolic diameter: 55.49 (8.64) mm • Indexed LV end-systolic diameter: 18.5 (3.04) mm/m^2 • Indexed LV end-diastolic diameter: 29.99 (5.78) mm/m^2 • Effective regurgitant orifice area: 43.97 (22.53) m^2 • Regurgitant volume: 72.46 (30.87) ml • Resting E/e' ratio: 14.09 (5.37) • Resting indexed left atrial volume: 41.96 (16.87) ml/m^2 • Resting systolic pulmonary artery pressure: 38.49 (9.12) mmHg **Exercise testing:** • Exercise heart rate: 127.0 (14.54) bpm • Exercise systolic blood pressure: 181.0 (32.09) mmHg • Exercise diastolic blood pressure: 83.99 (14.55) mmHg • Maximal exercise workload: 102 (33.38) W • Effective regurgitant orifice area: 48.43 (27.67) m^2 • Severe MR: 79 (68.7%) • Regurgitant volume: 74.42 (35.46) ml • Exercise E/e' ratio: 14.74 (4.55) • Exercise indexed left atrial volume: 44.48 (16.69) ml/m^2 • Exercise systolic pulmonary artery pressure: 59.97 (16.07) mmHg **Population source:** Consecutive patients matching inclusion criteria between January 2008 and June 2011 at two valve disease outpatient clinics in Canada and Belgium.

Reference	Magne 2014[157]
Prognostic variable	Absence of contractile reserve (exercise-induced improvement in global longitudinal strain <2%) Presence of contractile reserve (exercise-induced improvement in global longitudinal strain ≥2%; referent) Exercise echocardiography: Patients performed symptom-limited graded bicycle exercise test in a semi-supine position on a tilting exercise table. Initial workload of 25 W was maintained for 2 min, after which the workload increased by 25 W every 2 min. Blood pressure and 12-lead ECG were recorded every 2 min. 2D and Doppler echocardiography images were available throughout the test.
Confounders	Variables included in the MV analyses: 1. age, sex, exercise regurgitant volume, exercise systolic pulmonary arterial pressure, exercise E/e' ratio, resting BNP level and LV contractile reserve based on global longitudinal strain (exercise-induced improvement in global longitudinal strain ≥2%). 2. LV ejection fraction, LV end-systolic diameter, indexed left atrial volume, pulmonary hypertension and LV contractile reserve based on global longitudinal strain (exercise-induced improvement in global longitudinal strain ≥2%). Multiple models with further confounders added sequentially were reported but the one that adjusted for the most confounders was extracted. In addition, a further model including echocardiographic variables reported in guidelines as useful in determining need for surgery was reported. This was also extracted as it contained a different set of confounders to the other models reported in the study. Key confounders in protocol: one of the pre-specified confounders listed in the protocol (coronary artery disease) was an exclusion criterion for the study. However, the other three pre-specified confounders were not mentioned in the study and not included in the multivariate analysis.
Outcomes and effect sizes	**Cardiac events (cardiovascular death, mitral valve surgery indicated by symptoms or LV dysfunction, or hospitalisation for acute pulmonary oedema or congestive heart failure) – medically managed – not explicitly stated but valve surgery captured as part of the outcome** 1. **HR 2.27 (95% CI 1.05 to 4.76) for absence vs. presence of contractile reserve on exercise – adjusted for age, sex, exercise regurgitant volume, exercise systolic pulmonary arterial pressure, exercise E/e' ratio and resting BNP level** 2. **HR 1.6 (95% CI 1.1 to 2.3) for absence vs. presence of contractile reserve on exercise – adjusted for LV ejection fraction, LV end-systolic diameter, indexed left atrial volume and pulmonary hypertension** Note: study reported the HR with absence of contractile reserve as the referent. To be more consistent with the protocol, this has been inverted so that results are reported with presence of contractile reserve being the referent. Though contractile reserve as assessed by LVEF was also reported, the study did not provide multivariate analysis results for this definition of contractile reserve and has therefore not been extracted. During follow-up, 41% patients experienced a cardiac event, leading to event-free survival results of 61±6% and 56±5% at 2- and 3-years, respectively. 36 had mitral valve surgery due to occurrence of symptoms (n=15), LV dilatation/dysfunction (n=4) or for both

Reference	Magne 2014[157]
	symptoms and LV dilatation/dysfunction (n=17). 11 patients had an event other than surgery (1 resuscitated sudden cardiac death, 7 hospitalisations for congestive heart failure, 1 syncope associated with fast atrial fibrillation and 2 acute pulmonary oedema). LV longitudinal myocardial function was evaluated with quantification of resting and exercise global longitudinal strain using 2D speckle tracking analysis. Exercise echocardiography acquisitions for the measurement of GLS and LVEF were performed before the end of exercise at a heart rate between 90 and 110 bpm. LV contractile reserve was evaluated using two most recently validated methods in patients with primary MR. Presence of contractile reserve was defined as: 1) exercise-induced improvement in LVEF ≥4% or 2) exercise-induced improvement in global longitudinal strain ≥2%. Follow-up was obtained from interviews with patients, physicians or next of kin every 6-12 months. Cardiac events were defined as cardiovascular death, mitral valve surgery (only when indicated by symptoms or LV dysfunction according to current guidelines) and hospitalisation for acute pulmonary oedema or congestive heart failure). Surgery performed only based on pulmonary hypertension being present was not considered to be an event. At the end of the study, patients with a last follow-up >6 months were re-evaluated by telephone by physicians or next of kin. Follow-up was complete in 100% patients. Mean (SD) follow-up: 24 (21) months.
Comments, risk of bias and indirectness	Note: risk of bias and indirectness rating below apply to both of the MV model results reported. Risk of bias: 1. Study participation — HIGH 2. Study attrition — LOW 3. Prognostic factor measurement — LOW 4. Outcome Measurement — LOW 5. Study confounding — HIGH 6. Statistical analysis — HIGH 7. Other risk of bias — LOW OVERALL RISK OF BIAS — VERY HIGH Indirectness: • Population – not limited to asymptomatic severe MR as includes some with asymptomatic moderate MR. 63% reported to be asymptomatic severe MR.

Reference	Magne 2014[157]
	• Confounders – though coronary artery disease was an exclusion criterion for this study, the other three pre-specified confounders in the protocol are not mentioned as being excluded or adjusted for in the multivariate analysis (downgraded for this in risk of bias so not downgraded further for indirectness)

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Reference	Magne 2015[152]
Study type and analysis	Prospective cohort study Cox proportional hazards regression Belgium, France, Canada
Number of participants and characteristics	N=102 Exercise pulmonary hypertension (SPAP >60 mmHg), n=59 No exercise pulmonary hypertension (SPAP ≤60 mmHg), n=43 Asymptomatic or mildly symptomatic degenerative moderate or severe mitral regurgitation that underwent mitral valve surgery – 81% severe MR. Proportion asymptomatic/mildly symptomatic unclear. Though patients with moderate MR at baseline exercise stress echocardiography were included, they were only operated on when severe MR developed, according to guidelines. **Inclusion criteria:** Moderate or severe degenerative MR (effective regurgitant orifice area ≥20 mm^2 and/or regurgitant volume ≥30 ml); asymptomatic or mildly symptomatic patients (NYHA function class ≤II); preserved LV ejection fraction (>60%); normal LV end-systolic diameter (<45 mm); in sinus rhythm; and mitral valve surgery performed during follow-up with class I or class IIa indication. **Exclusion criteria:** Those with mitral valve surgery performed for class IIb indication; suspected coronary artery disease; ST segment changes during exercise; exercise-induced wall motion abnormalities; and >mild concomitant valvular stenosis or regurgitation. **Values listed below are presented as mean (SD) or number (%)**

Reference	Magne 2015[152]
	Patient characteristics: • Age: 64 (12) years • Male sex, 69 (68%) • Renal failure, 4 (4%) • Systemic hypertension, 47 (46%) • Diabetes, 7 (7%) • Hypercholesterolaemia, 33 (32%) • Resting heart rate: 72 (12) bpm • Resting systolic blood pressure: 138 (20) mmHg • Resting diastolic blood pressure: 78 (10) mmHg • LV end-systolic diameter: 34 (6) mm • LV end-diastolic diameter: 55 (8) mm • LV ejection fraction, median (IQR): 71 (66; 76)% • Regurgitant volume, median (IQR): 66 (53; 90) ml • Effective regurgitant orifice area, median (IQR): 40 (35; 60) mm^2 • Left atrium surface, median (IQR): 35 (24; 76) cm^2 • E/e' ratio: 14 (5) • Systolic pulmonary artery pressure, median (IQR): 36 (30; 42) mmHg • Severe MR, 83 (81%) **Exercise testing:** • Exercise workload: 80 (33) W • Exercise heart rate: 122 (17) bpm • Exercise systolic blood pressure: 174 (32) mmHg • Exercise diastolic blood pressure, median (IQR): 90 (75-90) • LV ejection fraction: 71 (9)% • Regurgitant volume, median (IQR): 75 (58; 98) ml • Effective regurgitant orifice area, median (IQR): 50 (40; 73) mm^2 • Systolic pulmonary artery pressure: 63 (18) mmHg • Severe MR, 83 (81%)

Reference	Magne 2015[152]
	• Change in regurgitant volume, median (IQR): +2 (-9; +14) ml • Change in effective regurgitant orifice area, median (IQR): +8 (0; +20) mm^2 • Change in systolic pulmonary artery pressure, median (IQR): +25 (+14; +33) mmHg **Population source:** Consecutive patients prospectively included between July 2007 and August 2012 across three centres in Belgium, France and Canada.
Prognostic variable	Exercise pulmonary hypertension (SPAP >60 mmHg) No exercise pulmonary hypertension (SPAP ≤60 mmHg; referent) SPAP was derived from the regurgitant jet of tricuspid regurgitation using systolic transtricuspid pressure gradient calculated by modified Bernoulli equation and addition of 10 mmHg for right atrial pressure. Right atrial pressure assumed to be constant from rest to exercise. Resting and exercise pulmonary hypertension were defined as SPAP >50 mmHg and SPAP >60 mmHg, respectively. Exercise testing: All patients had resting and exercise Doppler echocardiography performed at time of inclusion in the study. Patients performed symptom-limited graded bicycle exercise test in semi-supine position on tilting exercise table. Initial workload was 25 W maintained for 2 min. Workload was increased by 25 W every 2 min. Blood pressure and 12-lead ECG were recorded every 2 min.
Confounders	Variables included in the multivariate analysis: age, sex, LVEF, baseline NYHA class and exercise pulmonary hypertension (SPAP >60 mmHg) Multiple models with different confounders included were reported and the one with the most confounders included was extracted. Though there were two with the same number of confounders (one including baseline NYHA class and the other including preoperative NYHA class), there was an error in the reported CIs for the model that included preoperative NYHA class. Therefore, the model with the above listed confounders was extracted. Key confounders in protocol: suspected coronary artery disease was an exclusion criterion, though 9% did have concomitant coronary artery bypass grafting performed. The remaining three confounders were not mentioned as exclusion criteria and were not adjusted for in the analysis.
Outcomes and effect sizes	**Postoperative cardiovascular events (postoperative cardiovascular death, cardiovascular hospitalisation, stroke or atrial fibrillation) – postoperative as all underwent mitral valve surgery to be included** **HR 2.0 (95% CI 1.2 to 4.3) for exercise pulmonary hypertension (SPAP >60 mmHg) vs. no exercise pulmonary hypertension (SPAP ≤60 mmHg)**

Reference	Magne 2015[152]
	Note: mitral valve repair was performed in 80 (78%) patients. The remaining (n=22, 22%) received mitral valve replacement, of which 50% received a biological prosthesis. The occurrence of AF was separated into early AF (within 48 h following surgery) and late AF (>48 h following surgery). During follow-up, 28 patients (27%) experienced a cardiovascular events: 4 cardiovascular deaths; 3 cardiac-related hospitalisations; 4 strokes; 5 early atrial fibrillation; and 14 late atrial fibrillation. Overall postoperative cardiac event-free survival was 80±4%, 79±4%, 79±4% and 71±6% at 1, 2, 3 and 5 years, respectively. Those with exercise pulmonary hypertension (SPAP >60 mmHg) had lower event-free survival compared with those without exercise pulmonary hypertension: 75±6% vs. 88±5% (1 year); 73±6% vs. 88±5% (3 years); and 60±8% vs. 88±5% (5 years). Last follow-up information was obtained from interviews with the patients or physicians. Range of follow-up: 10-128 months Mean (SD) follow-up: 50 (23) months. Follow-up was complete in 100% of patients.
Comments, risk of bias and indirectness	Risk of bias: 1. Study participation — HIGH 2. Study attrition — LOW 3. Prognostic factor measurement — LOW 4. Outcome Measurement — LOW 5. Study confounding — HIGH 6. Statistical analysis — LOW 7. Other risk of bias — LOW OVERALL RISK OF BIAS — VERY HIGH Indirectness: • Population – not limited to asymptomatic severe MR but includes some with asymptomatic moderate MR. 81% reported to be asymptomatic severe MR. Also includes asymptomatic or minimally symptomatic patients, and unclear proportion within each of these groups. • Confounders – though coronary artery disease was an exclusion criterion for this study, the other three pre-specified confounders in the protocol are not mentioned as being excluded or adjusted for in the multivariate analysis (downgraded for this in risk of bias so not downgraded further for indirectness)

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Reference	Messika-Zeitoun 2006[166]
Study type and analysis	Prospective cohort study Cox proportional hazards model USA
Number of participants and characteristics	N=134 Functional capacity (peak VO_2) on exercise ≤84% of predicted for age, weight and gender, n=26 Functional capacity (peak VO_2) on exercise >84% of predicted for age, weight and gender, n=108 Asymptomatic moderate or severe organic mitral regurgitation – 57% were severe MR and mean regurgitant volume was consistent with severe disease as defined in the study (regurgitant volume ≥60 ml/beat). However, mean effective regurgitant orifice was not consistent with severe MR as defined in the study (effective regurgitant orifice ≥40 mm^2). **Inclusion criteria:** Pure, isolated mitral regurgitation and regurgitant volume ≥30 ml/beat; quantitative assessment of cardiac remodelling and LV systolic and diastolic function; performed maximal exercise test (achieved heart rate goal of ≥85% of age-predicted peak heart rate or stopped due symptoms of dyspnoea, exhaustion or hypotension); and echocardiography and cardiopulmonary exercise testing performed during same episode of care without intervening clinical change. **Exclusion criteria:** Age ≥90 years; history of congestive heart failure; rheumatic mitral stenosis of any degree; moderate or more severe lung disease; exercise-limited by angina; exercise testing stopped due to ischaemic or severe arrhythmia. **Values listed below are presented as mean (SD) or number (%)** **Patient characteristics:** • Age: 63 (14) years • Male sex, 85 (63%) • Body mass index: 26 (4) kg/m^2 • Mitral valve prolapse (with or without flail), 125 (93%) • Severe MR, 77 (57%) • Beta-blocker therapy, 31 (23%)

Reference	Messika-Zeitoun 2006[166]
	• Atrial fibrillation, 6 (5%) • Heart rate: 66 (10) bpm • Forward stroke volume: 79 (16) ml • Cardiac index: 2.7 (0.5) l/min/m^2 • Systolic pulmonary artery pressure: 32 (9) mmHg • End-diastolic volume index: 108 (20) ml/m^2 • End-systolic volume index: 29 (10) ml/m^2 • LV mass/volume: 1.1 (0.2) g/ml • LV ejection fraction: 73 (6)% • End-systolic wall stress/end-systolic volume index: 5.3 (1.4) g/cm^2 per ml/m^2 • Left atrium index: 68 (26) ml/m^2 • Regurgitant volume: 68 (24) ml/beat • Effective regurgitant orifice: 35 (14) mm^2 • E/A ratio: 1.4 (0.5) • Deceleration time: 213 (40) ms • E/E' ratio: 12 (5) • Systolic blood pressure: 128 (17) mmHg • Diastolic blood pressure: 74 (11) mmHg **Exercise testing:** • Minute ventilation (VE)/carbon dioxide production (VCO_2) slope: 30 (4) • Peak heart rate: 150 (22) bpm • Peak heart rate ≥85% predicted, 115 (86%) • Peak systolic blood pressure: 183 (24) mmHg • Peak diastolic blood pressure: 77 (13) mmHg • Double product: 27,426 (5,203) • Exercise duration: 10 (3) min • Peak O_2 pulse: 13 (4) ml/beat • O_2 pulse increase: 9 (3) ml/beat • Absolute peak VO_2: 26 (6) ml/kg/min

Reference	Messika-Zeitoun 2006[166]
	• Percent of predicted peak VO_2: 96 (16)% **Population source:** Consecutive patients matching inclusion criteria between 1998 and 2004, single centre in USA.
Prognostic variable	Functional capacity (peak VO_2) on exercise ≤84% of predicted for age, weight and gender Functional capacity (peak VO_2) on exercise >84% of predicted for age, weight and gender (referent) Exercise testing: Symptom-limited treadmill exercise testing with respiratory gas exchange analysis was performed with modified Bruce protocol (2 min workloads, 2 W/min increments in work). ECGs were continuously monitored, and blood pressure assessed at last 30 seconds of each 2 min workload. Patients encouraged to exercise until exhaustion. Peak VO_2 was the highest averaged 30 second VO_2 during exercise and was expressed as absolute peak VO_2 or normalised peak Vo_2 (percent of age, gender and weight predicted). Functional capacity was considered to be markedly reduced with a peak VO_2 ≤84% of predicted and was not available to patient physicians who conducted clinical management.
Confounders	Variables included in the multivariate analysis: age, effective regurgitant orifice, gender, LV ejection fraction and reduced functional capacity on exercise (peak VO_2 ≤84%). Key confounders in protocol: moderate or severe lung disease excluded, but other three confounders listed in protocol not excluded from study or included in the multivariate analysis.
Outcomes and effect sizes	**Clinical events (death, heart failure or new severe symptoms, or new atrial arrhythmia) or indication for surgery – medically managed – not explicitly stated but surgery captured as part of the outcome** **HR 1.53 (95% CI 1.10 to 2.09) for functional capacity (peak VO_2) on exercise ≤84% vs. >84% of predicted for age, weight and gender – conservative management** Note: results are reported in the study as RR rather than HR, but the method used for analysis was described as Cox proportional hazards analysis, suggesting it should in fact be a HR not RR. Results have therefore been reported as a HR. During follow-up, clinical events occurred in 20 patients (3 deaths, 15 congestive heart failure or occurrence of severe symptoms and 2 atrial arrhythmias). Rate of clinical events at 3 years was higher in those with reduced functional capacity (peak VO_2 on exercise ≤84% predicted) compared with those with normal function capacity (36±14% vs. 13±4%). A total of 42 patients underwent surgery for mitral regurgitation (12 for new symptoms and 30 based on patient and physician preference, supported by severity of MR, LV and LA remodelling, and progression. Patients with reduced functional capacity on exercise also displayed a higher 3-year incidence of mitral surgery compared with those with normal function capacity (53±12% vs. 29±5%). Overall, clinical events or mitral surgery occurred in 50 patients at 4 years. Patients with reduced functional capacity demonstrated higher 3-year rate of combined end-point (clinical event or surgery) compared with normal functional capacity (66±11% vs. 29±5%). Mean (SD) follow-up: 2.2 (1.3) years.

Reference	Messika-Zeitoun 2006[166]
Comments, risk of bias and indirectness	Risk of bias: 1. Study participation HIGH 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement LOW 5. Study confounding HIGH 6. Statistical analysis LOW 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH Indirectness: • Population – not limited to asymptomatic severe MR but includes some with asymptomatic moderate MR. 57% reported to be asymptomatic severe MR. • Prognostic factor – threshold of <60% in protocol for exercise capacity but threshold of 84% used in this study. • Confounders – though moderate or severe lung disease excluded, other three confounders listed in the protocol are not mentioned as exclusion criteria or adjusted for in the multivariate analysis (downgraded for this in risk of bias so not downgraded further for indirectness).

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Reference	Moss 2014[171]
Study type and analysis	Retrospective cohort study Cox proportional hazards model Thailand
Number of participants and characteristics	N=125 Absence of contractile reserve on stress testing, n=70 Presence of contractile reserve on stress testing, n=55

Reference	Moss 2014[171]
	Asymptomatic/mildly symptomatic moderate-severe or severe mitral regurgitation (functional MR) – 81% severe MR. Note, also includes ~18% that were symptomatic, in NYHA class III or IV. Both ischaemic and idiopathic cardiomyopathy patients were included. **Inclusion criteria:** LV ejection fraction ≤35%; severe functional mitral regurgitation (MR grade 3+ by echocardiography); underwent dobutamine stress echocardiography for assessment of contractile reserve. **Exclusion criteria:** Concomitant significant aortic valve disease; mitral valve replacement; dobutamine stress echocardiography performed as a primary indication for inducible ischaemic of a known coronary stenosis; degree of MR improved to <3 at time of dobutamine testing; and LV ejection fraction improved to >35% at time of dobutamine testing. **Values listed below are presented as mean (SD) or number (%)** **Patient characteristics:** • Age: 60 (12) years • Male sex, 96 (77%) • NYHA class 3 or 4, 22 (17.6%) • Diabetes mellitus, 36 (28.8% • Hypertension, 52 (41.6%) • Coronary artery disease, 64 (51.2%) • ACE inhibitors or ARBs, 118 (94.4%) • Beta-blockers, 116 (92.8%) • Spironolactone, 105 (84.0%) • Furosemide, 111 (88.8%) • Resynchronisation therapy, 14 (11.2%) • Sodium: 139.6 (2.9) • eGFR: 58.5 (21.1) • LV end-diastolic dimension: 70.1 (8.7) mm • LV ejection fraction: 23.8 (6.4)% • Right ventricular dysfunction, 66 (52.8%)

Reference	Moss 2014[171]
	• Severe MR, 101 (80.8%) • Moderate or severe tricuspid regurgitation, 30 (24.0%) • Systolic pulmonary artery pressure: 44.5 (13.2) mmHg **Dobutamine stress testing:** • Peak blood pressure response: 143.5 (26.9) mmHg • Peak dobutamine heart rate: 106.7 (30.1) bpm **Population source:** Those matching inclusion criteria undergoing assessment of contractile reserve between May 1999 and November 2005. Identified from Cardiac Echo laboratory database and characteristics and outcomes reviewed using Heart Function Clinic database and clinical charts with linkage to the British Columbia Vital Statistic Database.
Prognostic variable	Absence of contractile reserve on stress testing Presence of contractile reserve on stress testing (improvement in global left ventricular function of ≥10% compared to baseline; referent) Dobutamine testing: Dobutamine infusion started at 10 or 20 µg/kg/min and imaged acquired at rest, low-dose, peak-dose and recovery phases. Atropine was administered (up to 1.8 mg) to increase heart rate at discretion of supervising physician. Contractile reserve was defined as improvement in global left ventricular function of ≥10% compared to baseline value. Stress testing was stopped when 85% of predicted maximum heart rate was achieved. Test terminated prematurely if any of the following occurred: severe chest pain, new wall motion abnormality (more than two segments), ST segment shift >2 mm with a new wall motion abnormality, significant hypotension (>40 mmHg fall in systolic blood pressure), or other intolerable side effects. LV ejection fraction was measured using biplane method of discs where feasible and was measured visually where it was not. Physicians did have access to the dobutamine test results.
Confounders	Variables were included in multivariate analysis based on significance on univariate analyses and clinical importance: age, baseline LV ejection fraction, NYHA class, moderate/severe tricuspid regurgitation and presence/absence of contractile reserve. Key confounders in protocol: none of the confounders specified in the protocol are mentioned as either exclusion criteria or confounders adjusted for in the multivariate analysis.
Outcomes and effect sizes	**All-cause mortality or requirement for heart transplant – medically or surgically managed – surgery not included in the final MV model** **HR 2.94 (95% CI 1.32 to 6.67) for absence vs. presence of contractile reserve.**

Reference	Moss 2014[171]
	Note: surgery was not included in the final MV model due to not being significant on univariate, therefore it may be contributing to outcomes. Results for the HR in the study are reported with absence of contractile reserve as the referent. To better match our protocol, the HR and Cis have been inverted so that the results are presented with presence of contractile reserve as the referent. Within 5 years, 24 of those without contractile reserve had died or required heart transplantation, while 7 of those with contractile reserve had died or required heart transplantation. A total of 18 with contractile reserve and 13 without contractile reserve underwent surgery within 5 years (19 combined coronary artery bypass grafting and mitral valve surgery, 9 mitral valve surgery alone and 3 coronary artery bypass grafting alone). Probability of heart transplant-free survival at 5 years was 87.2% for those with contractile reserve and 64.5% for those without contractile reserve. Median follow-up: 1,871 days.
Comments, risk of bias and indirectness	Risk of bias: 1. Study participation HIGH 2. Study attrition LOW 3. Prognostic factor measurement HIGH 4. Outcome Measurement LOW 5. Study confounding HIGH 6. Statistical analysis HIGH 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH Indirectness: • Population– not limited to asymptomatic severe MR as includes some with moderate-severe disease, and also some with mild symptoms (proportion unclear). In addition, ~18% are reported to be symptomatic and in NYHA classes III or IV. • Confounders – have not adjusted for any of the pre-specified confounders listed in the protocol or mentioned them as exclusion criteria so these factors may be contributing to the results (downgraded for this in risk of bias so not downgraded further for indirectness) • Outcomes – have not provided results separately for those receiving medical management only and those that received surgery during follow-up as hoped to do in the protocol, in addition, adjustment for surgery has not been included in the multivariate analysis.

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D.4 Symptomatic non-severe mitral regurgitation

Reference	Lancellotti 2005[124]
Study type and analysis	Prospective cohort study Cox proportional hazards regression Belgium

Number of participants and characteristics	N=161
	Increase in ERO by ≥13 mm^2 (severe status unmasked in response to exercise), n=48
	Increase in ERO by <13 mm^2, no increase or decrease (severe status not unmasked in response to exercise), n=113
	
	Symptomatic non-severe mitral regurgitation (functional MR secondary to heart failure) – includes mild-severe MR, with ~32% having severe MR at rest.
	
	Inclusion criteria:
	Chronic ischaemic left ventricular dysfunction (ejection fraction ≤45%); at least mild functional mitral regurgitation; underwent quantitative Doppler echocardiography; and stable for at least 2 months.
	
	Exclusion criteria:
	Technically inadequate echocardiogram; more than trivial aortic regurgitation; intraventricular conduction abnormality; functional class IV; history of myocardial infarction <6 months; and atrial fibrillation or flutter or evidence of inducible ischaemic on upright exercise test.
	
	Values listed below are presented as mean (SD) or number (%)
	Patient characteristics:
	• Age: 65 (11) years
	• Male sex, 66%
	• NYHA class:
	  ○ I, 18 (11.2%)
	  ○ II, 104 (64.6%)
	  ○ III, 39 (24.2%)
	• Site of previous myocardial infarction
	  ○ Anterior, 68 (42.2%)

Reference	Lancellotti 2005[124]
	○ Inferior, 72 (44.7%) ○ Anterior and inferior, 21 (13.0%) • Medications ○ ACE inhibitors, 125 (77.6%) ○ Diuretics, 70 (43.5%) ○ Beta-blockers, 99 (61.5%) ○ Nitrates, 58 (36.0%) ○ Spironolactone, 38 (23.6%) • History of systemic arterial hypertension, 71 (44.1%) • Diabetes, 39 (24.2%) • Previous surgical revascularisation, 29 (18.0%) • Heart rate: 74 (12) bpm • Systolic arterial pressure: 128 (15) mmHg • LV end-diastolic volume: 144 (30) ml/m^2 • LV end-systolic volume: 93 (25) ml/m^2 • LV ejection fraction: 36 (7)% • Mitral deceleration time: 178 (51) ms • Effective regurgitant orifice: 17 (9) mm^2 • Effective regurgitant orifice ≥20 mm^2, 51 (32%) • Transtricuspid pressure gradient: 27 (10) mmHg **Exercise testing:** difference in values between rest and exercise • Heart rate: 39 (14) bpm • Systolic arterial pressure: 27 (17) mmHg • LV end-diastolic volume: 0.51 (18) ml/m^2 • LV end-systolic volume: -8.3 (17) ml/m^2 • LV ejection fraction: 8 (7)% • Effective regurgitant orifice: 8 (10) mm^2 • Effective regurgitant orifice ≥20 mm^2, 48 (30%) • Transtricuspid pressure gradient: 19 (13) mmHg

Reference	Lancellotti 2005[124]
	Population source: Consecutive patients undergoing exercise Doppler echocardiography between May 1998 and December 2003, in Belgium.
Prognostic variable	Increase in ERO by ≥13 mm^2 (severe status unmasked in response to exercise) Increase in ERO by <13 mm^2, no increase or decrease (severe status not unmasked in response to exercise; referent) Exercise testing: Beta-blockers were stopped 24 h prior to test. Symptom-limited graded bicycle exercise test performed in semi-supine position on tilting exercise table. After initial workload of 25 W for 6 min, workload was increased every 2 min by 25 W. Blood pressure and 12-lead ECG were recorded every 2 min. 2D and Doppler echocardiograms were available throughout the test. Quantification of mitral regurgitation was performed by quantitative Doppler method using mitral and aortic stroke volumes and the proximal isovelocity surface area method. The results of the two methods were averaged for calculation of the effective regurgitant orifice.
Confounders	Unmodified forward-selection stepwise analysis was used to select variables for the multivariable analysis. Variable with most significant association with outcome was included in the first model. At second and subsequent steps, remaining variables were evaluated and most significant included if it significantly improved the prediction of the outcome. Algorithm ceased to select variables when there was no further significant improvement in prediction of whole model The following variables were included in the final model: • Cardiac death outcome: ERO increase ≥13 mm^2 on exercise, ERO≥20 mm^2 at rest and transtricuspid pressure gradient difference (continuous) • Hospital admission for heart failure outcome: ERO increase ≥13 mm^2 on exercise, transtricuspid pressure gradient difference (continuous) and LV end-systolic volume at rest (continuous) Key confounders in protocol: none of those listed in protocol included as confounders in the MV analysis or excluded from the study. None mentioned in study characteristics tables either.
Outcomes and effect sizes	**Cardiac death – under medical management as censored at time of cardiac surgery if performed** **HR 5.0 (95% CI 1.9 to 13.0) for ERO increase ≥13 mm^2 on exercise vs. ERO increase <13 mm^2, no increase or decrease on exercise** Note: follow-up was censored at time of cardiac surgery if eventually performed. Patients with exercise-induced increase in ERO ≥13 mm^2 had a higher mortality (74% vs. 22.5%). **Hospital admission for heart failure – under medical management as censored at time of cardiac surgery if performed**

Reference	Lancellotti 2005[124]
	HR 3.6 (95% CI 1.4 to 9.2) for ERO increase ≥13 mm^2 on exercise vs. ERO increase <13 mm^2, no increase or decrease on exercise Note: follow-up was censored at time of cardiac surgery if eventually performed. During follow-up, 26 patients were readmitted for cardiac decompensation. <u>Further information on all outcomes</u> During follow-up, 20 patients received cardiac surgery [4 cardiac transplants, 16 mitral annuloplasty (n=14) and/or bypass surgery (n=12)]. Of these, 3 patients died and all 20 receiving cardiac surgery were censored at the time of surgery. Of those treated medically (n=141), 23 died (n=7 sudden death, n=9 refractory heart failure and n=7 myocardial infarction), 22 were admitted for worsening heart failure, 4 had non-fatal myocardial infarction, 11 developed unstable angina, 7 were treated by cardiac resynchronisation therapy and/or implantable defibrillator and 1 had permanent right ventricular stimulation for high degree AV-block. Of the 23 that died, 4 were admitted and discharged from hospital for heart failure prior to their death. Range of follow-up: 2-53 months. Mean (SD) follow-up: 35 (11) months. Median (IQR) follow-up: 36 (30-42) months.
Comments, risk of bias and indirectness	Risk of bias: <u>For cardiac death outcome</u> 1. Study participation — HIGH 2. Study attrition — LOW 3. Prognostic factor measurement — LOW 4. Outcome Measurement — HIGH 5. Study confounding — HIGH 6. Statistical analysis — HIGH 7. Other risk of bias — LOW OVERALL RISK OF BIAS — VERY HIGH <u>For hospitalisation for heart failure outcome</u> 1. Study participation — HIGH 2. Study attrition — LOW 3. Prognostic factor measurement — LOW 4. Outcome Measurement — HIGH

Reference	Lancellotti 2005[124]	
	5. Study confounding	HIGH
	6. Statistical analysis	HIGH
	7. Other risk of bias	LOW
	OVERALL RISK OF BIAS	VERY HIGH
	Indirectness: <u>For cardiac death outcome</u> • Population – ~32% had symptomatic severe MR, as opposed to symptomatic non-severe (mild or moderate) MR at rest. Therefore, some with increase of ERO ≥13 may have already been within the severe range. Mean ERO at rest is consistent with non-severe MR as <20 mm^2. • Prognostic factor – ERO increase of ≥13 mm^2 may not represent increase to severe range in all patients, particularly in very mild cases of MR at rest. • Confounders – have not adjusted for any of the pre-specified confounders listed in the protocol or mentioned them as exclusion criteria so these factors may be contributing to the results (downgraded for this in risk of bias so not downgraded further for indirectness) <u>For hospitalisation for heart failure outcome</u> • Population – ~32% had symptomatic severe MR, as opposed to symptomatic non-severe (mild or moderate) MR at rest. Therefore, some with increase of ERO ≥13 may have already been within the severe range, or may be higher number with severe MR at rest in the no increase group compared with increase group. Mean ERO at rest is consistent with non-severe MR as <20 mm^2. • Prognostic factor – ERO increase of ≥13 mm^2 may not represent increase to severe range in all patients, particularly in very mild cases of MR at rest. • Confounders – have not adjusted for any of the pre-specified confounders listed in the protocol or mentioned them as exclusion criteria so these factors may be contributing to the results (downgraded for this in risk of bias so not downgraded further for indirectness)	

1

D.5 Any valve disease combined

Reference	Bhattacharyya 2013[21]
Study type and analysis	Prospective cohort study (some uncertainty about whether prospective or retrospective)

Reference	Bhattacharyya 2013[21]
	Cox regression analysis – appears to be multivariate as 'independent predictors' mentioned, but this is unclear. Reported as a hazard ratio. UK

Number of participants and characteristics	N=100
	Positive exercise test, n=32
	Negative exercise test, n=68
	
	Various types of valve disease assessed by stress echocardiography (exercise echocardiography), including symptomatic non-severe mitral regurgitation, asymptomatic severe mitral regurgitation, symptomatic non-severe mitral stenosis, asymptomatic severe mitral stenosis, asymptomatic severe aortic stenosis and asymptomatic severe aortic regurgitation
	
	Inclusion criteria:
	Poorly described. Includes those with any of the above-mentioned valve disease presentations.
	
	Exclusion criteria:
	Not reported.
	
	Values listed below are presented as mean (SD) or number (%)
	
	Type of valve disease:
	• Mitral regurgitation, 52 (52%)
	  ○ Functional, 30 (30%)
	  ○ Degenerative, 22 (22%)
	• Mitral stenosis, 8 (8%)
	• Aortic stenosis, 34 (34%)
	  ○ Low-flow low-gradient, 26 (26%)
	  ○ Asymptomatic severe, 8 (8%)
	• Aortic regurgitation, 6 (6%)
	
	Patient characteristics:

Reference	Bhattacharyya 2013[21]

	• Valve intervention following stress echocardiography: all 25 interventions were in those with positive stress echocardiogram (n=32)
	  ○ Surgical aortic valve replacement, 6%
	  ○ Mitral valve replacement, 8%
	  ○ Transcatheter aortic valve implantation, 7%
	  ○ Percutaneous mitral valve repair, 4%
	• Age: 67.26 (16.27) years
	• Male/female: 46/54 (46%/54%)
	• Smoker, 10 (10%)
	• Hypertension, 40 (40%)
	• Diabetes, 13 (13%)
	• Hyperlipidaemia, 27 (27%)
	• Previous coronary artery bypass grafting, 11 (11%)
	• Previous percutaneous coronary intervention, 14 (14%)
	• LVEF: 54.72 (13.71) %
	• LV end-diastolic diameter: 5.32 (0.66) cm
	• Interventricular septum thickness: 1.04 (0.19) cm
	• Left atrial diameter, 4.38 (0.82) cm
	
	No variables measured on dobutamine or exercise testing reported.
	
	Population source: consecutive patients undergoing stress echocardiography at single echocardiography laboratory between October 2010 and May 2012. Appears to be prospective but this is unclear.

Prognostic variable	Positive stress echocardiography Negative stress echocardiography (referent) A positive stress echocardiogram was defined differently for each different type of valve disease presentation: • Symptomatic non-severe MR: increase in severity to severe – effective orifice area ≥0.4 cm^2 (organic) or ≥0.2 cm^2 (functional) • Asymptomatic severe MR: increase in pulmonary artery systolic pressure >60 mmHg • Symptomatic non-severe MS: increase in mean transmitral gradient ≥15 mmHg or estimated pulmonary artery systolic pressure ≥60 mmHg

Reference	Bhattacharyya 2013[21]
	• Asymptomatic severe MS: increase in mean transmitral gradient ≥15 mmHg or estimated pulmonary artery systolic pressure ≥60 mmHg or symptom development • Asymptomatic severe AS: increase in mean transaortic gradient ≥20 mmHg • Asymptomatic severe AR: lack of increase in LVEF ≥5% or exercise-induced reduction in LVEF Exercise testing: Symptom-limited bicycle test was performed in semi-supine position on tilting exercise bicycle. Exercise performed starting at workload of 25W. Workload increased by 25W every 2 min. 2D and Doppler echocardiography measurements made at rest and at peak exercise. Test stopped if limiting symptoms (chest pain and dyspnoea) or significant adverse haemodynamic changes occurred. Dobutamine stress testing: Performed for low-flow, low-gradient, low-ejection fraction severe aortic stenosis (valve area ≤1.0 cm^2, mean gradient <40 mmHg and LVEF ≤40%. After echocardiography, dobutamine infusion of 5 µg/kg/min was initiated. Dose was increased in 5 µg/kg/min increments every 5 min to a max. dose of 20 µg/kg/min. Measurements were taken at each stage of the process.
Confounders	Variables that demonstrated significance were included in the multivariate analysis: variables included in the multivariate analysis unclear. Key confounders in protocol: confounders adjusted for unclear and may not have included those in the protocol.
Outcomes and effect sizes	**<u>Admission for worsening heart failure or death – includes both medically and surgically managed patients</u>** **HR 15.49 (95% CI 4.18 to 57.38) for positive vs. negative stress echocardiogram result** Note: does not appear to have adjusted for type of treatment (surgery or medical). Assumed to be multivariate analysis as they mention 'independent predictors', but this is not explicitly stated. Worsening heart failure was defined as worsening NYHA functional class or signs of fluid retention. A total of 24 events occurred during follow-up (12 admissions for heart failure and 12 deaths). Of the 32 with a positive test result, 18 (56.3%) had an event compared with 6 (8.8%) in those with a negative stress echocardiogram. Of the 32 patients with a positive test, 25 (78.1%) underwent a valve intervention, with 12 having an event prior to the intervention. The remaining 7 with a positive test result were medically managed, with 6 having an event. Median (IQR) follow-up: 12.6 (8.8-17.5) months

Reference	Bhattacharyya 2013[21]
Comments, risk of bias and indirectness	Risk of bias: 1. Study participation HIGH 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement LOW 5. Study confounding VERY HIGH 6. Statistical analysis HIGH 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH Indirectness: • Population – different valve disease presentation types combined as a single group rather than presenting separately as in protocol • Prognostic factors – various factors listed in protocol combined under positive exercise echocardiogram rather than being reported separately • Outcomes – medically and surgically managed patients included rather than presenting separately and has not adjusted or this in the analysis. • Confounding factors – unclear if any key confounders listed in protocol were excluded or adjusted for in multivariate analysis so may have differed between the prognostic factor groups (downgraded for this in risk of bias so not downgraded further for indirectness)

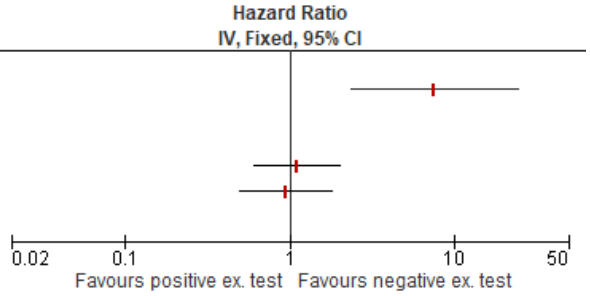
1
2

Appendix E – Forest plots

E.1 Asymptomatic severe aortic stenosis

Figure 2: Positive/abnormal versus negative/normal exercise test in asymptomatic moderate or severe AS – symptoms in daily life or sudden death

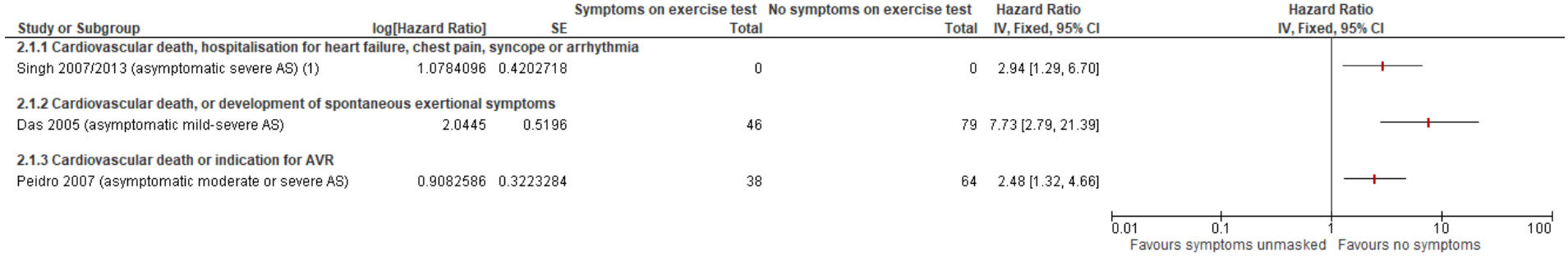
Study or Subgroup	log[Hazard Ratio]	SE	Positive exercise test Total	Negative exercise test Total	Hazard Ratio IV, Fixed, 95% CI
1.1.1 Symptoms in daily life or sudden death					
Amato 2001 (severe asymptomatic AS)	2.0281	0.6	44	22	7.60 [2.34, 24.63]
1.1.2 Symptoms, AVR or CV death					
Lancellotti 2010-1 (asympt. mod. or severe AS) (1)	0.0953	0.3071	69	94	1.10 [0.60, 2.01]
Lancellotti 2010-2 (asympt. mod. or severe AS) (2)	-0.0513	0.3319	32	94	0.95 [0.50, 1.82]



Footnotes
(1) Abnormal test: significant symptoms, ≥2 mm ST segment depression relative to baseline; rise in systolic BP <20 mmHg or a fall in blood pressure, or complex ventricular arrhythmias.
(2) Abnormal test: symptoms, rise in systolic BP <20 mmHg or a fall in blood pressure, ventricular tachycardia or >4 premature ventricular complexes in a row

Note: Forest the two Lancellotti 2010 data points are from separate studies – outcomes are the same but definition of the prognostic factor differs slightly, as does the definition of the outcome (significant symptoms in one study and just symptoms in another). Not pooled due to these reasons and the fact that the studies may overlap in terms of patients included as number and type of events reported in the two studies are very similar.

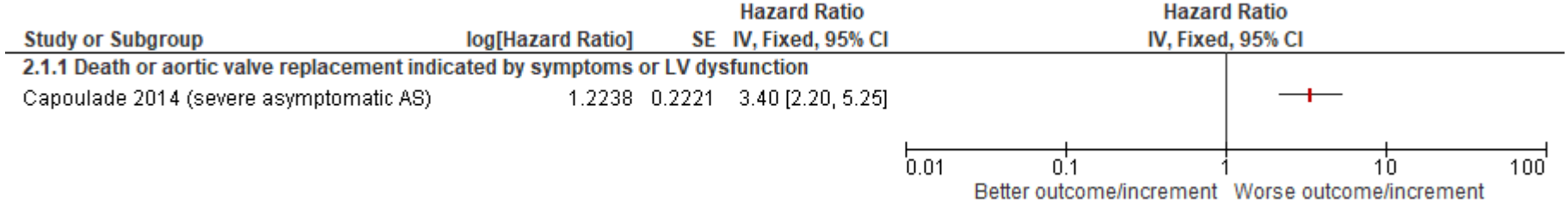
Figure 3: Symptoms unmasked versus no symptoms on exercise in asymptomatic AS



Footnotes
(1) Number in each group not reported

1

Figure 4: Absolute difference of BNP levels from rest to exercise (per 100 pg/ml increase from rest) in asymptomatic severe AS

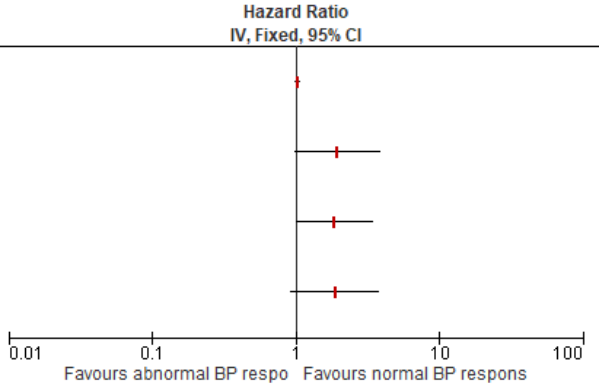


Note: left-hand side indicates fewer events with every 100 pg/ml increase in BNP from rest, while right-hand side indicates that with every 100 pg/ml increase in BNP from rest an increased number of events are observed (worse outcome).

2

Figure 5: Abnormal versus normal response of blood pressure to exercise in asymptomatic moderate or severe AS t

Study or Subgroup	log[Hazard Ratio]	SE	Abnormal BP response Total	Normal BP response Total	Hazard Ratio IV, Fixed, 95% CI
4.1.1 Cardiovascular death or development of spontaneous exertional symptoms					
Das 2005 (asymptomatic mild-severe AS) (1)	0.0198026	0.0176002	29	96	1.02 [0.99, 1.06]
4.1.2 Cardiovascular death or indication for AVR					
Peidro 2007 (asymptomatic moderate or severe AS) (2)	0.6678294	0.3419006	27	75	1.95 [1.00, 3.81]
4.1.3 Aortic valve replacement (severe AS subgroup)					
Chambers 2019 (moderate or severe asymptomatic AS) (3)	0.6206	0.3137	42	60	1.86 [1.01, 3.44]
4.1.4 Revealed symptoms developing spontaneously or during follow-up (mod or severe asymptomatic on exercise test at baseline)					
Chambers 2019 (moderate or severe asymptomatic AS) (4)	0.6259	0.3604	113	193	1.87 [0.92, 3.79]

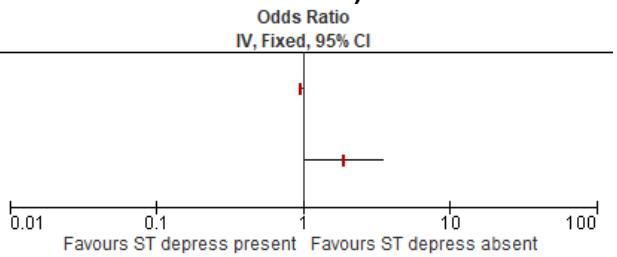


Footnotes
(1) Abnormal BP response: reduction or no increase compared to rest
(2) Abnormal BP response: drop in systolic BP ≥10 mmHg vs.<10 mmHg on exercise
(3) Abnormal BP response: sustained reduction ≥20 mmHg below previous stage or baseline level
(4) Abnormal BP response: sustained reduction ≥20 mmHg below previous stage or baseline level

1

Figure 6: ST depression present versus absent on exercise in asymptomatic AS (majority moderate or severe disease)

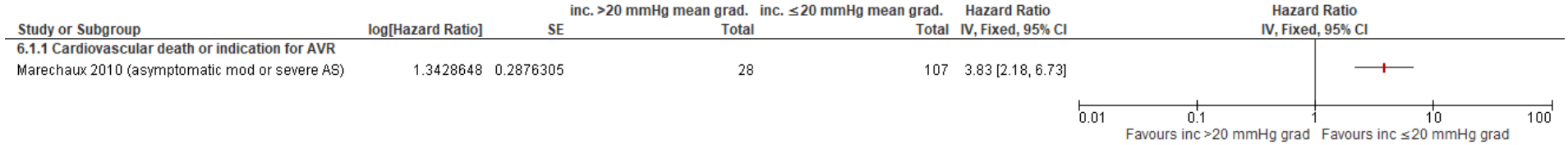
Study or Subgroup	log[Odds Ratio]	SE	ST depression present Total	ST depression absent Total	Odds Ratio IV, Fixed, 95% CI
5.1.1 Development of spontaneous exertional symptoms of CV death					
Das 2005 (asymptomatic mild-severe AS) (1)	-0.0305	0.0181367	33	92	0.97 [0.94, 1.01]
5.1.2 Cardiovascular death or indication for AVR					
Peidro 2007 (asymptomatic moderate or severe AS) (2)	0.6365768	0.31058	43	59	1.89 [1.03, 3.47]



Footnotes
(1) ST depression: ≥2 mm vs. <2 mm on exercise
(2) Downsloping ST depression: >1 mm vs. ≤1 mm on exercise

1

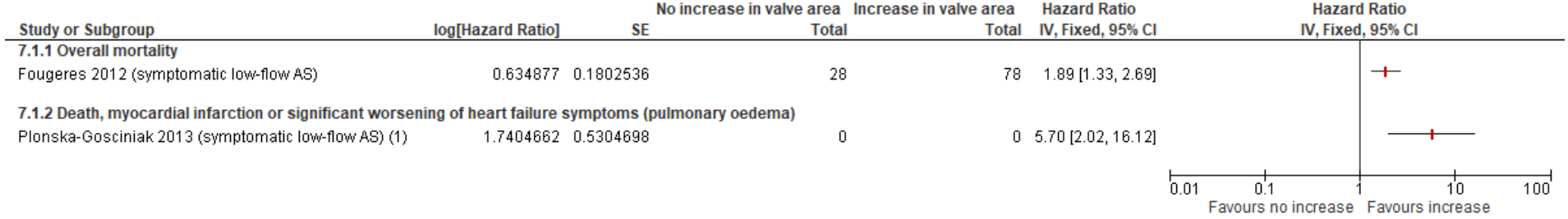
Figure 7: Mean gradient increase >20 mmHg versus ≤20 mmHg on exercise echocardiography in asymptomatic/minimally symptomatic moderate or severe AS



2

E.2 Symptomatic low-flow aortic stenosis

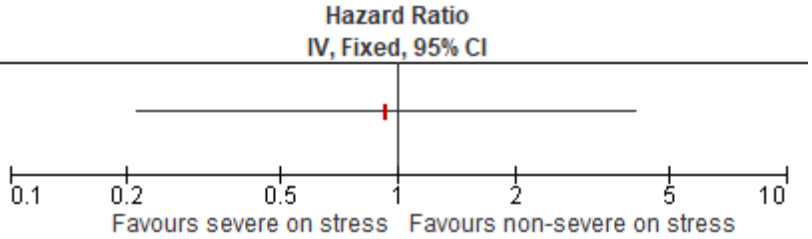
Figure 8: No increase versus increase in valve area on dobutamine stress echocardiography testing in symptomatic low-flow AS



Footnotes
(1) Number in each group not reported

Figure 9: Increase versus no increase of mean gradient to within severe range (≥40 mmHg) on dobutamine stress echocardiography testing in low-flow low-gradient AS

Study or Subgroup	log[Hazard Ratio]	SE	Hazard Ratio IV, Fixed, 95% CI
8.1.1 Mortality at 4 years			
Annabi 2018 (low-flow AS, likely symptomatic) (1)	-0.0726	0.7532	0.93 [0.21, 4.07]



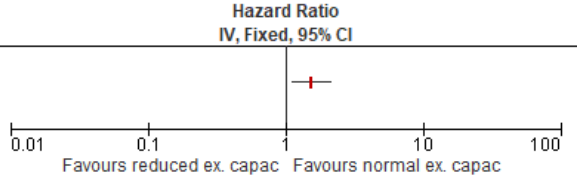
Footnotes
(1) Number in each group not reported

1

E3 Asymptomatic severe mitral regurgitation

Figure 10: Exercise capacity (VO_2 max) ≤84% versus >84% predicted in asymptomatic moderate or severe organic MR

Study or Subgroup	log[Hazard Ratio]	SE	Reduced exercise capacity Total	Normal exercise capacity Total	Hazard Ratio IV, Fixed, 95% CI
10.1.1 Clinical events (death, HF or new severe symptoms, or new atrial arrhythmia) or indication for surgery					
Messika-Zeitoun 2006 (asympt mod or severe MR)	0.4252677	0.1637382	26	108	1.53 [1.11, 2.11]



3

Figure 11: Increase of systolic pulmonary artery pressure to >60 mmHg versus ≤60 mmHg on exercise echocardiography (exercise pulmonary hypertension) in asymptomatic moderate or severe MR, 60% with severe disease

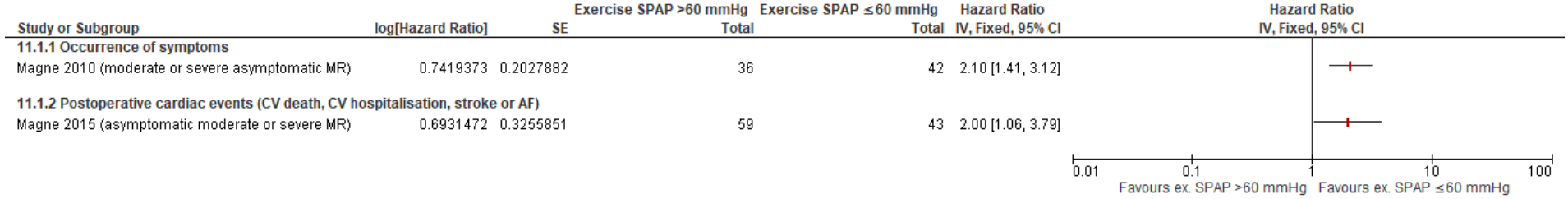
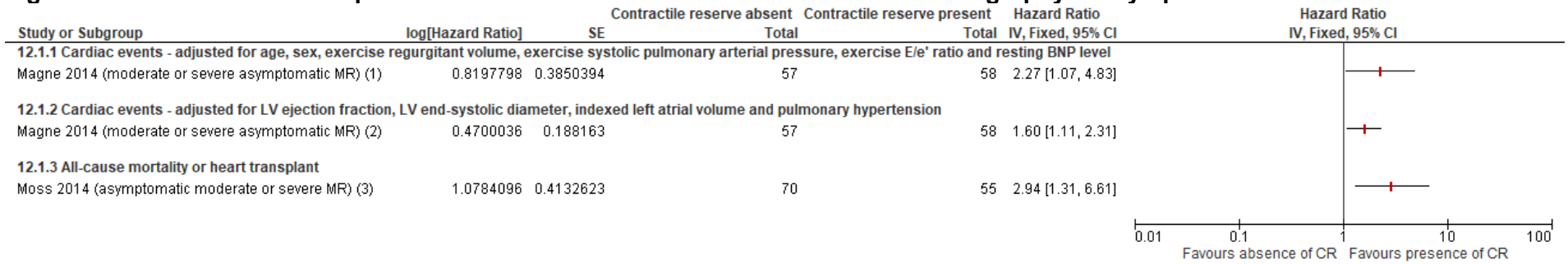


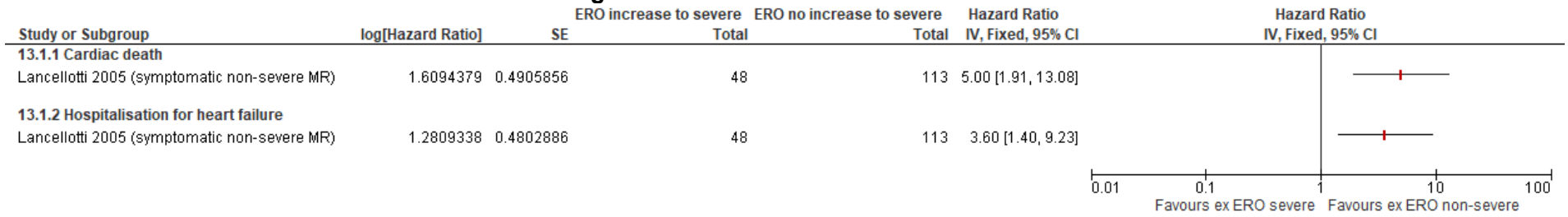
Figure 12: Absence versus presence of contractile reserve on exercise echocardiography in asymptomatic moderate or severe MR



Footnotes
(1) Absence of CR: <2% improvement in global longitudinal strain
(2) Absence of CR: <2% improvement in global longitudinal strain
(3) Absence of CR: <10% improvement in global left ventricular function

E.4 Symptomatic non-severe mitral regurgitation

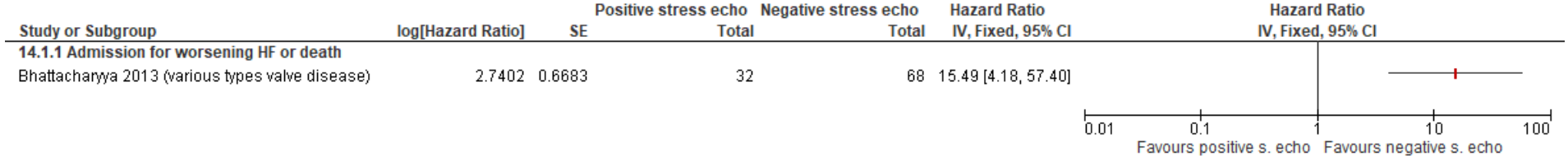
Figure 13: Increase in effective regurgitant orifice by ≥13 mm² on exercise echocardiography in symptomatic non-severe MR, includes mild-severe MR with ~32% having severe MR at rest



2

E.5 Any valve disease combined

Figure 14: Positive versus negative exercise echocardiogram in various valve disease presentations (symptomatic non-severe mitral regurgitation, asymptomatic severe mitral regurgitation, symptomatic non-severe mitral stenosis, asymptomatic severe mitral stenosis, asymptomatic severe aortic stenosis and asymptomatic severe aortic regurgitation)



4

Appendix F – GRADE tables

F.1 Asymptomatic severe aortic stenosis

Table 19: Clinical evidence profile: positive versus negative exercise test (various definitions qualify)

Quality assessment							No of patients		Effect	Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations (including publication bias where possible)	Positive ex. test	Negative ex. test	Relative (95% CI)	
Symptoms in daily life or sudden death (adjusted HR) - (asymptomatic severe aortic stenosis; mean age 49.7 years; medically managed). Follow-up mean 14.77 months.										
1	Cohort study	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	44	22	Adjusted HR: 7.60 (2.34 to 24.63)[3]	VERY LOW
Development of significant symptoms, need for aortic valve replacement or cardiac-related death (adjusted HR) - (asymptomatic moderate or severe aortic stenosis; mean age 70 years; medically managed and censored at cardiac surgery). Follow-up mean 20 months.										
1	Cohort study	very serious[1]	no serious inconsistency	serious[4]	very serious[5]	none	69	94	Adjusted HR: 1.10 (0.60 to 2.0)[6]	VERY LOW
Development of symptoms, need for aortic valve replacement or cardiac-related death (adjusted HR) - (asymptomatic moderate or severe aortic stenosis; mean age 67.5 years; medically managed and censored at cardiac surgery). Follow-up median 20.3 months.										
1	Cohort study	very serious[1]	no serious inconsistency	serious[4]	very serious[5]	none	32	94	Adjusted HR: 0.95 (0.49 to 1.80)[7]	VERY LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2]Prognostic factor indirectness - combination of various prognostic factors listed in the protocol, rather than providing prognostic information for each one separately (symptoms on exercise, reduction in BP >20 mmHg, ST depression and complex ventricular arrhythmia)
[3]Methods: multivariable analysis, not including key confounders in protocol but adjusted for the following: age, aortic valve area and exercise testing.
[4]Population indirectness – not limited to asymptomatic severe AS as includes some with asymptomatic moderate AS; prognostic factor indirectness – combination of various prognostic factors listed in the protocol, rather than providing prognostic information for each one separately
[5]95% CIs cross null line and are very wide
[6]Methods: multivariable analysis, not including key confounders in protocol but adjusted for the following: gender; systemic arterial compliance; peak aortic velocity; valvulo-arterial impedance; LV longitudinal strain; LA area index; mitral E wave; mitral E/A ratio; and abnormal exercise test result.
[7]Methods: multivariable analysis, not including key confounders in protocol but adjusted for the following: gender; B-type natriuretic peptide; abnormal response to exercise; aortic valve area; peak aortic velocity; aortic mean pressure gradient; left atrial area index; peak systolic velocity; peak early diastolic annular velocity; peak late diastolic annular velocity; and early diastolic filling/annular velocity.

Table 20: Clinical evidence profile: symptoms unmasked versus no symptoms on exercise

Quality assessment							No patients		Effect	Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations (including publication bias where possible)	Symptoms unmasked	No symptoms	Relative (95% CI)	
Cardiovascular death, typical AS symptoms indicating aortic valve replacement referral or major adverse cardiac events (hospitalisation for heart failure, chest pain, syncope or arrhythmia) (adjusted HR) - (asymptomatic severe aortic stenosis; mean age for severe subgroup unclear but is 66.2 years for whole cohort; medically managed as indication for aortic valve replacement captured as part of the outcome). Follow-up median 374 days.										
1	Cohort study	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	123		Adjusted HR: 2.94 (1.29 to 6.70)[2]	LOW
Development of spontaneous exertional symptoms or cardiovascular death (adjusted OR) - (asymptomatic mild-severe aortic stenosis with majority being moderate or severe disease; mean age 65.0 years; medically managed – not explicitly stated but no mention of any aortic valve operations being performed). Follow-up mean 12 months.										
1	Cohort study	very serious[1]	no serious inconsistency	serious[3]	no serious imprecision	none	46	79	Adjusted OR: 7.73 (2.79 to 21.39)[4]	VERY LOW
Cardiovascular death or indication for AVR (adjusted OR) - (asymptomatic moderate or severe aortic stenosis; mean age 64.35 years; medically managed as indication for AVR captured as part of outcome). Follow-up median 10.7 months.										
1	Cohort study	very serious[1]	no serious inconsistency	serious[5]	no serious imprecision	none	38	64	Adjusted OR: 2.48 (1.32 to 4.66)[6]	VERY LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2]Methods: multivariable analysis, not including key confounders in protocol but adjusted for the following: sex, NT-proBNP, aortic valve area index, cardiac magnetic resonance LV mass/volume ratio, myocardial perfusion reserve and positive exercise tolerance test
[3]Population indirectness - includes asymptomatic mild to severe AS, but majority are either moderate or severe (92%). Only 42% of the population represented asymptomatic severe AS as specified in the protocol.
[4]Methods: multivariable analysis, not including any of the key confounders in the protocol. However, one of the pre-specified confounders (lung disease) was an exclusion criterion for the study. The following variables were adjusted for: total exercise time, exercise-limiting symptoms, peak transaortic velocity, effective orifice area, abnormal blood pressure response and ST segment depression.
[5]Population indirectness - not limited to asymptomatic severe AS as includes some with asymptomatic moderate AS - 87% of the population have severe AS.
[6]Methods: multivariable analysis, but unclear which variables included in the analysis. One of the confounders listed in the protocol was an exclusion criterion (lung disease) and the remaining were not mentioned. The following variables may have been adjusted for in the multivariate model, but this is very unclear: symptoms on exercise testing, drop in systolic blood pressure and downsloping ST segment depression >1 mm.

Table 21: Clinical evidence profile: absolute difference of BNP levels from rest to exercise (per 100 pg/ml increase from rest)

Quality assessment							No of patients	Effect	Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations (including publication bias where possible)		Relative (95% CI)	
Death or aortic valve replacement indicated by symptom development or LV dysfunction (adjusted HR) - (asymptomatic severe aortic stenosis; mean age 68.0 years; medically managed as AVR captured as part of the outcome). Follow-up mean 1.5 years.									
1	Cohort study	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	157	Adjusted HR: 3.40 (2.20 to 5.23)[3]	VERY LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2]Prognostic factor indirectness - difference between exercise and rest BNP levels as a continuous variable, rather than a dichotomous increase in BNP levels vs. no increase in BNP levels on exercise compared with rest
[3]Methods: multivariable analysis, not including key confounders in protocol but adjusted for the following: age, gender, resting mean gradient, resting valvulo-arterial impedance, resting indexed left atrial area, resting BNP level and exercise-induced increases in heart rate, mean gradient and valvulo-arterial impedance

Table 22: Clinical evidence profile: abnormal versus normal response of blood pressure to exercise

Quality assessment							No of patients		Effect	Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations (including publication bias where possible)	Abnormal BP response	Normal BP response	Relative (95% CI)	
Development of spontaneous exertional symptoms or cardiovascular death (adjusted OR) - (asymptomatic mild-severe aortic stenosis with majority being moderate or severe disease; mean age 65.0 years; medically managed – not explicitly stated but no mention of any aortic valve operations being performed). Follow-up mean 12 months.										
1	Cohort study	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	29	96	Adjusted OR: 1.02 (0.99 to 1.06)[4]	VERY LOW
Cardiovascular death or indication for aortic valve replacement (adjusted OR) - (asymptomatic moderate or severe aortic stenosis; mean age 64.35 years; medically managed as aortic valve replacement captured as part of the outcome). Follow-up mean 10.7 months.										

1	Cohort study	very serious[1]	no serious inconsistency	serious[5]	serious[3]	none	27	75	Adjusted OR: 1.95 (1.00 to 3.81)[6]	VERY LOW
Aortic valve replacement during follow-up (adjusted HR) – (asymptomatic severe aortic stenosis patients; mean age 69.0 years; medically managed up until indication for developed). Mean follow-up for the whole cohort was 34.9 months and was not reported separately for the individual severities.										
1	Cohort study	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	42	60	Adjusted HR 1.86 (1.01 to 3.44)[7]	LOW
Revealed symptoms developing spontaneously or during follow-up (adjusted HR) - (asymptomatic moderate or severe aortic stenosis that remained asymptomatic on baseline exercise test; mean age of the subgroup unclear but 65.0 years for whole cohort; medically managed as no indication for AVR unless symptoms developed). Mean follow-up for the whole cohort was 34.9 months and was not reported separately for the individual severities.										
1	Cohort study	very serious[1]	no serious inconsistency	serious[8]	serious[3]	none	113	193	Adjusted HR: 1.87 (0.92 to 3.79)[7]	VERY LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2]Population indirectness - includes asymptomatic mild to severe AS, but majority are either moderate or severe (92%). Only 42% of the population represented asymptomatic severe AS as specified in the protocol.
[3]95% CIs cross the null line
[4]Methods: abnormal BP response defined as reduction or no increase compared to rest; multivariable analysis, not including any of the key confounders in the protocol. However, one of the pre-specified confounders (lung disease) was an exclusion criterion for the study. The following variables were adjusted for: total exercise time, exercise-limiting symptoms, peak transaortic velocity, effective orifice area, abnormal blood pressure response and ST segment depression.
[5]Population indirectness – not limited to asymptomatic severe AS as includes some with asymptomatic moderate AS – 87% of the population have severe AS. Prognostic factor indirectness – threshold used in study differs to that specified in protocol, as ≥10 mmHg drop in systolic blood pressure on exercise is used rather than ≥20 mmHg drop on exercise.
[6]Methods: abnormal BP response defined as drop in SBP ≥10 mmHg on exercise; multivariable analysis, but unclear which variables included in the analysis. One of the confounders listed in the protocol was an exclusion criterion (lung disease) and the remaining were not mentioned. The following variables may have been adjusted for in the multivariate model, but this is very unclear: symptoms on exercise testing, drop in systolic blood pressure and downsloping ST segment depression >1 mm.
[7]Methods: abnormal BP response defined as sustained reduction ≥20 mmHg on exercise; multivariable analysis, including one of the key confounders in the protocol (coronary artery disease). Two other confounders listed in the protocol were exclusion criteria and the remaining one was not mentioned. The following variables were adjusted for: rapid early rise in heart rate, age, sex, hypertension, Doppler stroke volume, mean pressure gradient, abnormal blood pressure response and coronary artery disease.
[8]Population indirectness - includes moderate or severe AS patients that were asymptomatic at baseline and remained asymptomatic on baseline exercise testing, not limited to asymptomatic severe AS

Table 23: Clinical evidence profile: ST depression present versus absent on exercise

Quality assessment							No of patients		Effect	Quality
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations (including publication bias where possible)**	**ST depression present**	**ST depression absent**	**Relative (95% CI)**	

Development of spontaneous exertional symptoms or cardiovascular death (adjusted OR) - (asymptomatic mild-severe aortic stenosis with majority being moderate or severe disease; mean age 65.0 years; medically managed – not explicitly stated but no mention of any aortic valve operations being performed). Follow-up mean 12 months.										
1	Cohort study	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	33	92	Adjusted OR: 0.97 (0.94 to 1.01)[4]	VERY LOW
Cardiovascular death or indication for AVR (adjusted OR) - (asymptomatic moderate or severe aortic stenosis; mean age 64.35 years; medically managed as indication for AVR captured as part of outcome). Follow-up median 10.7 months.										
1	Cohort study	very serious[1]	no serious inconsistency	serious[5]	no serious imprecision	none	43	59	Adjusted OR: 1.89 (1.03 to 3.47)[6]	VERY LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2]Population indirectness - includes asymptomatic mild to severe AS, but majority are either moderate or severe (92%). Only 42% of the population represented asymptomatic severe AS as specified in the protocol. Prognostic factor indirectness - unclear if coronary disease is absent, which was specified in the protocol as important when this prognostic factor was used.
[3]95% CIs cross null line
[4]Methods: ST depression defined as ≥2mm; multivariable analysis, not including any of the key confounders in the protocol. However, one of the pre-specified confounders (lung disease) was an exclusion criterion for the study. The following variables were adjusted for: total exercise time, exercise-limiting symptoms, peak transaortic velocity, effective orifice area, abnormal blood pressure response and ST segment depression.
[5]Population indirectness - not limited to asymptomatic severe AS as includes some with asymptomatic moderate AS - 87% of the population have severe AS. Prognostic factor indirectness - threshold used in study differs to that specified in protocol, as >1 mmHg ST segment depression on exercise is used rather than >2 mm ST segment depression on exercise. Coronary disease is also not absent in all patients, which was specified in the protocol as important when interpreting this prognostic factor. The study states that ST segment depression >1 mm did not identify those patients with associated coronary disease.
[6]Methods: downsloping ST depression defined as ≥1mm; multivariable analysis, but unclear which variables included in the analysis. One of the confounders listed in the protocol was an exclusion criterion (lung disease) and the remaining were not mentioned. The following variables may have been adjusted for in the multivariate model, but this is very unclear: symptoms on exercise testing, drop in systolic blood pressure and downsloping ST segment depression >1 mm.

Table 24: Clinical evidence profile: Mean gradient increase >20 mmHg versus ≤20mmHg on exercise echocardiography

Quality assessment							No of patients		Effect	Quality
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations (including publication bias where possible)**	**Gradient increase >20mmHg**	**Gradient increase ≤20mmHg**	**Relative (95% CI)**	
Cardiovascular death or need for aortic valve replacement due to symptoms or LV systolic dysfunction (adjusted HR) - (asymptomatic/minimally symptomatic moderate or severe aortic stenosis; mean age 64.0 years; medically managed as AVR captured as part of outcome). Follow-up mean 20 months.										
1	Cohort study	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	28	107	Adjusted HR: 3.83 (2.18 to 6.73)[3]	VERY LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

[2]Population indirectness - not limited to asymptomatic severe AS but includes some with asymptomatic moderate AS, with the proportion being unclear.
[3]Methods: multivariable analysis, not including any of the key confounders in the protocol. However, two of the confounders listed in the protocol were exclusion criteria for the study (coronary artery disease and lung disease). The variables including in the analysis were unclear, but the HR appears to have been adjusted for the following: age ≥65 years, diabetes, rest systolic blood pressure >135 mmHg, LV hypertrophy, rest mean gradient >35 mmHg, increase in mean gradient on exercise >20 mmHg and exercise LV ejection fraction <70%.

F.2 Symptomatic low-flow aortic stenosis

Table 25: Clinical evidence profile: no increase in valve area versus no increase in valve area on dobutamine stress echocardiography testing

Quality assessment							No of patients		Effect	Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations (including publication bias where possible)	Increase in valve area	No increase in valve area	Relative (95% CI)	
Overall mortality (adjusted HR) - (symptomatic low-flow aortic stenosis; median age 76.0 years; conservative management for >6 months). Follow-up median 25 months.										
1	Cohort study	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	28	78	Adjusted HR: 1.89 (1.33 to 2.69)[3]	LOW
Death, myocardial infarction or significant worsening of heart failure symptoms (pulmonary oedema) (adjusted HR) - (symptomatic low-flow aortic stenosis, ~12.8% appear to be asymptomatic as are in NYHA class I; mean age 59.0 years; includes patients that were managed medically or surgically and does not include this as a confounder to adjust for in the MV analysis). Follow-up mean 353 days.										
1	Cohort study	very serious[1]	no serious inconsistency	serious[4]	no serious imprecision	none	39		Adjusted HR: 5.70 (2.02 to 16.12)[5]	VERY LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2]Prognostic factor indirectness - in the subgroup with no contractile reserve it was not possible to determine whether it was true-severe AS or pseudo-severe AS based on increase/no increase in valve area and the study reports them as a separate, third group. However, for the multivariate analysis the no contractile reserve subgroup is combined with true-severe AS and it is unclear whether this group experienced an increase in valve area or not. Based on study characteristics table, only small increases in valve area reported in the no contractile reserve group so may all have shown no increase as well as in the true-severe AS group, though this is unclear
[3]Methods: multivariable analysis, not including any of the key confounders in the protocol. The variables included in the analysis were: pseudo-severe AS, logistic EuroSCORE, baseline mean pressure gradient and male sex.
[4]Population indirectness - not limited to symptomatic low-flow AS as appears to include some that are asymptomatic (NYHA class I) - 87% are symptomatic low-flow AS. Outcome indirectness - combines medically and surgically treated patients in the same analysis and has not included this as a confounding factor, whereas in the protocol ideally separate results for those medically and surgically treated could be extracted

[5]Methods: multivariable analysis, though confounders included in the reported multivariate analysis are unclear. May have included the following: aortic valve area at peak stress, absence of aortic valve area increase during stress, absence of contractile reserve and presence of significant coronary artery disease. If these were the included confounders, only one of those specified in the protocol has been included

Table 26: Clinical evidence profile: increase of mean gradient to within severe range (≥40 mmHg) versus no increase to within the severe range on dobutamine stress echocardiography testing

Quality assessment							No of patients		Effect	Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations (including publication bias where possible)	Severe on stress echo	Non-severe on stress echo	Relative (95% CI)	
Mortality (adjusted HR) - (low-flow low-gradient aortic stenosis, at least 40% symptomatic as NYHA class III or IV but unclear if remaining patients were symptomatic; mean age 73.0 years; medically managed subgroup). Follow-up mean 4 years.										
1	Cohort study	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	88		Adjusted HR: 0.93 (0.21 to 4.07)[4]	VERY LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2]Population indirectness - unclear if 60% not in NYHA class III or IV also had symptoms, so may not represent a symptomatic low-flow AS population specified in the protocol as may include some asymptomatic low-flow patients.
[3]95% CIs cross null line and intervals are very wide
[4]Methods: multivariable analysis, not including any of the key confounders in the protocol. The variables included in the analysis were: age, sex, functional capacity (Duke activity status index), kidney failure and LVEF at peak dobutamine stress.

F.3 Asymptomatic severe mitral regurgitation

Table 27: Clinical evidence profile: exercise capacity (VO_2 max) ≤84% predicted for weight, age and gender

Quality assessment	No of patients	Effect	Quality

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations (including publication bias where possible)	Total	Relative (95% CI)	
Clinical events (death, heart failure or new severe symptoms, or new atrial arrhythmia) or indication for surgery (adjusted HR) - (asymptomatic moderate or severe mitral regurgitation – 57% severe; mean age 63.0 years; medically managed as indication for surgery captured as part of the outcome). Follow-up mean 2.2 years.									
1	Cohort study	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	134	Adjusted HR: 1.53 (1.11 to 2.11)[3]	VERY LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2]Population indirectness - not limited to asymptomatic severe MR but includes some with asymptomatic moderate MR. 57% reported to be asymptomatic severe MR. Prognostic factor indirectness - threshold of <60% in protocol for exercise capacity but threshold of 84% used in this study.
[3]Methods: multivariable analysis, not including any of the key confounders in the protocol. Moderate or severe lung disease was an exclusion criterion for the study, but the other three confounders listed in the protocol were not mentioned. The variables included in the analysis were: age, effective regurgitant orifice, gender, LV ejection fraction and reduced functional capacity on exercise (peak VO2 ≤84%)

Table 28: Clinical evidence profile: increase of systolic pulmonary artery pressure to >60 mmHg on exercise echocardiography (exercise pulmonary hypertension)

Quality assessment							No of patients		Effect	Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations (including publication bias where possible)	Exercise SPAP >60 mmHg	Exercise SPAP ≤60 mmHg	Relative (95% CI)	
Development of symptoms during follow-up (adjusted HR) - (asymptomatic moderate or severe mitral regurgitation – 60% with severe disease; mean age 61.0 years; medically managed as symptom development was an indication for operation). Follow-up mean 19 months.										
1	Cohort study	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	36	42	Adjusted HR: 2.10 (1.41 to 3.12)[3]	VERY LOW
Postoperative cardiovascular events (CV death, CV hospitalisation, stroke or AF) (adjusted HR) - (asymptomatic or mildly symptomatic moderate or severe mitral regurgitation – 81% severe, proportion mildly symptomatic unclear; mean age 64.0 years; surgically managed). Follow-up mean 50 months.										
1	Cohort study	very serious[1]	no serious inconsistency	serious[4]	no serious imprecision	none	59	43	Adjusted HR: 2.00 (1.06 to 3.79)[5]	VERY LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2]Population indirectness - not limited to asymptomatic severe MR but includes some with asymptomatic moderate MR. 60% reported to be asymptomatic severe MR.

[3]Methods: multivariable analysis, not including any of the key confounders in the protocol. The variables included in the analysis were: age, sex, resting E-wave velocity, exercise left ventricular end-diastolic volume and exercise pulmonary hypertension (SPAP >60 mmHg).
[4]Population indirectness - not limited to asymptomatic severe MR but includes some with asymptomatic moderate MR. 81% reported to be asymptomatic severe MR. Also includes asymptomatic or minimally symptomatic patients, and unclear proportion within each of these groups.
[5]Methods: multivariable analysis, not including any of the key confounders in the protocol. Though suspected coronary artery disease was an exclusion criterion, some did have concomitant coronary artery bypass grafting performed with valve intervention. The variables included in the analysis were: age, sex, LVEF, baseline NYHA class and exercise pulmonary hypertension (SPAP >60 mmHg)

Table 29: Clinical evidence profile: absence versus presence of contractile reserve on exercise echocardiography

Quality assessment							No of patients		Effect	Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations (including publication bias where possible)	Absence of CR	Presence of CR	Relative (95% CI)	
Cardiac events (CV death, MV surgery, hospitalisation acute pulmonary oedema or CHF) (adjusted HR) - (asymptomatic moderate or severe primary mitral regurgitation – 63% severe; mean age 61.0 years; medically managed as valve surgery captured as part of outcome). Follow-up mean 24 months.										
1	Cohort study	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	57	58	Adjusted HR: 2.27 (1.07 to 4.83)[3]	VERY LOW
Cardiac events (CV death, MV surgery, hospitalisation acute pulmonary oedema or CHF) (adjusted HR) - (asymptomatic moderate or severe primary mitral regurgitation – 63% severe; mean age 61.0 years; medically managed as valve surgery captured as part of outcome). Follow-up mean 24 months.										
1	Cohort study	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	57	58	Adjusted HR: 1.60 (1.11 to 2.31)[4]	VERY LOW
All-cause mortality or heart transplant (adjusted HR) - (asymptomatic or mildly symptomatic moderate-severe or severe mitral regurgitation – 81% severe and ~18% that were symptomatic in NYHA class III or IV; mean age 60.0 years; medically or surgically managed combined and not included in MV analysis). Follow-up median 62 months.										
1	Cohort study	very serious[1]	no serious inconsistency	serious[5]	no serious imprecision	none	70	55	Adjusted HR: 2.94 (1.31 to 6.61)[6]	VERY LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2]Population indirectness - not limited to asymptomatic severe MR as includes some with asymptomatic moderate MR. 63% reported to be asymptomatic severe MR.
[3]Methods: absence of CR: <2% improvement in global longitudinal strain; multivariable analysis, not including any of the key confounders in the protocol. Coronary artery disease was an exclusion criterion but the other prespecified confounders in the protocol were not adjusted for. The variables included in the analysis were: age, sex, exercise regurgitant volume, exercise systolic pulmonary arterial pressure, exercise E/e' ratio, resting BNP level and LV contractile reserve based on global longitudinal strain (exercise-induced improvement in global longitudinal strain ≥2%).
[4]Methods: absence of CR: <2% improvement in global longitudinal strain; multivariable analysis, not including any of the key confounders in the protocol. Coronary artery disease was an exclusion criterion but the other prespecified confounders in the protocol were not adjusted for. The variables included in the analysis were: LV ejection fraction, LV end-systolic diameter, indexed left atrial volume, pulmonary hypertension and LV contractile reserve based on global longitudinal strain (exercise-induced improvement in global longitudinal strain ≥2%).

[5]Population indirectness - not limited to asymptomatic severe MR as includes some with moderate-severe disease, and also some with mild symptoms (proportion unclear). In addition, ~18% are reported to be symptomatic and in NYHA classes III or IV. Outcome indirectness - have not provided results separately for those receiving medical management only and those that received surgery during follow-up as set out in the protocol. In addition, adjustment for surgery has not been included in the multivariate analysis.
[6]Methods: absence of CR: <10% improvement in global left ventricular function; multivariable analysis, not including any of the key confounders in the protocol. The variables included in the analysis were: age, baseline LV ejection fraction, NYHA class, moderate/severe tricuspid regurgitation and presence/absence of contractile reserve.

F.4 Symptomatic non-severe mitral regurgitation

Table 30: Clinical evidence profile: increase in effective regurgitant orifice to severe range (increase ≥13 mm^2) versus no increase to severe range in symptomatic on exercise echocardiography in non-severe functional mitral regurgitation

Quality assessment							No of patients		Effect	Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations (including publication bias where possible)	ERO increase to severe	No ERO increase to severe	Relative (95% CI)	
Cardiac death (adjusted HR) - (symptomatic non-severe functional mitral regurgitation – includes mild-severe MR with ~32% having severe MR at rest; mean age 65.0 years; medically managed as patients censored from analysis if surgery performed). Follow-up mean 35 months.										
1	Cohort study	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	48	113	Adjusted HR: 5.0 (1.91 to 13.08)[3]	VERY LOW
Hospitalisation for heart failure (adjusted HR) - (symptomatic non-severe functional mitral regurgitation – includes mild-severe MR with ~32% having severe MR at rest; mean age 65.0 years; medically managed as patients censored from analysis if surgery performed). Follow-up mean 35 months.										
1	Cohort study	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	48	113	Adjusted HR: 3.60 (1.40 to 9.23)[4]	VERY LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2]Population indirectness - 32% had symptomatic severe MR rather than symptomatic non-severe MR at rest. Therefore, some with increase of ERO ≥13 mm^2 may have already been within the severe range. Mean ERO at rest is consistent with non-severe MR as <20 mm^2. Prognostic factor indirectness - ERO increase of ≥13 mm^2 may not represent increase to severe range in all patients, particularly in very mild cases of MR at rest.
[3]Methods: multivariable analysis, not including any of the key confounders in the protocol. The variables included in the analysis were: ERO increase ≥13 mm2 on exercise, ERO ≥20 mm2 at rest and transtricuspid pressure gradient difference
[4]Methods: multivariable analysis, not including any of the key confounders in the protocol. The variables included in the analysis were: ERO increase ≥13 mm2 on exercise, transtricuspid pressure gradient difference and LV end-systolic volume at rest

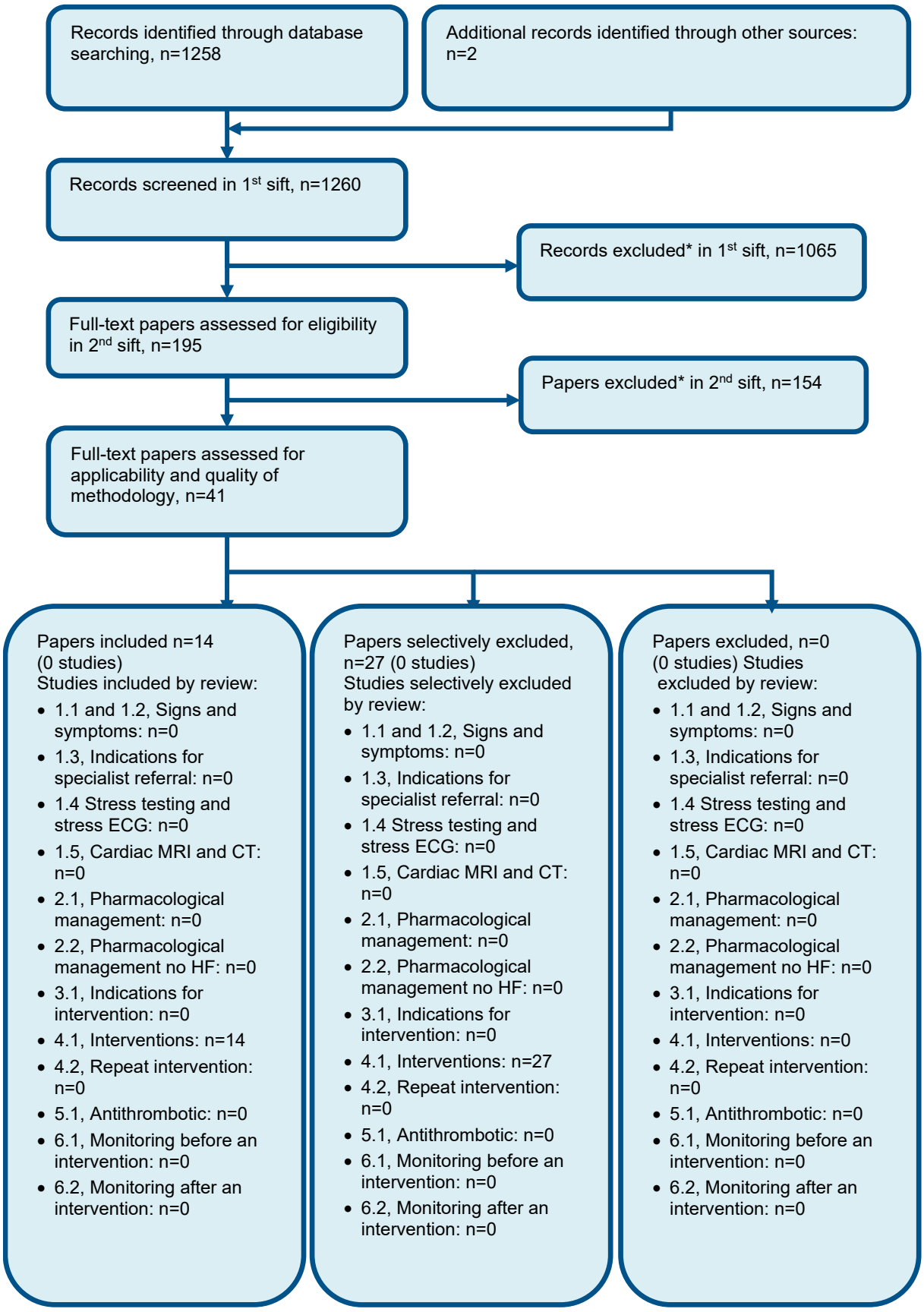
F.5 Any valve disease combined

Table 31: Clinical evidence profile: Positive versus negative exercise echocardiogram in a mixed HVD population

Quality assessment							No of patients		Effect	Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations (including publication bias where possible)	Positive exercise echo	Negative exercise echo	Relative (95% CI)	
Admission for worsening heart failure or death (adjusted HR) - (various valve disease presentations – symptomatic non-severe mitral regurgitation, asymptomatic severe mitral regurgitation, symptomatic non-severe mitral stenosis, asymptomatic severe mitral stenosis, asymptomatic severe aortic stenosis and asymptomatic severe aortic regurgitation; mean age 67.26 years; medically or surgically managed patients included, does not appear to have adjusted for surgery). Follow-up median 12.6 months.										
1	Cohort study	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	32	68	Adjusted HR: 15.49 (4.18 to 57.40)[3]	VERY LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2]Population indirectness - different valve disease presentation types combined as a single group rather than presenting separately as in protocol. Prognostic factor indirectness - various factors listed in protocol combined under positive exercise echocardiogram rather than being reported separately.
[3]Methods: multivariable analysis appears to have been performed as the study mentions independent predictors, however the variables included in the analysis are unclear.

1 Appendix G – Economic evidence study selection



* Non-relevant population, intervention, comparison, design or setting; non-English language

1

Appendix H – Economic evidence tables

None.

Appendix I – Health economic model

None.

1

1 Appendix J – Excluded studies

2 Clinical studies

3 Table 32: Studies excluded from the clinical review

Reference	Reason for exclusion
Abdul-Jawad Altisent 2017[1]	Incorrect prognostic factors - none matching protocol
Agricola 2005[2]	Incorrect outcomes - none matching protocol; incorrect analysis - no multivariate analysis.
Agricola 2008[3]	Incorrect population - severity and symptomatic status unclear; incorrect prognostic factors - do not match protocol or no results given.
Aguiar Rosa 2016[4]	Incorrect prognostic factors - none matching protocol
Alborino 2002[5]	Incorrect analysis - no prognostic effect sizes reported, only accuracy measures
Amer 2020[7]	Incorrect study design – no prognostic analysis
Anand 2020[8]	Incorrect study design - narrative review.
Ashikaga 2019[10]	Incorrect prognostic factors - none matching protocol
Awais 2009[11]	Incorrect study design - narrative review.
Badiani 2018[12]	Incorrect study design - narrative review.
Bakkestrom 2018[13]	Incorrect outcomes - none matching protocol
Banovic 2013[15]	Incorrect analysis - no prognostic effect sizes reported
Banovic 2020[14]	Incorrect outcomes - none matching protocol
Barbosa 2009[16]	Incorrect study design - no prognostic factor analysis; incorrect population: mostly moderate AR and mix of symptomatic and asymptomatic patients
Bartel 2013[17]	Incorrect study design - narrative review.
Ben-Dor 2012[18]	Incorrect population - symptomatic severe AS; incorrect prognostic factors - none on stress/exercise testing.
Bermejo 2003[19]	Incorrect prognostic factors - none matching protocol
Bertrand 2014[20]	Incorrect outcomes - none matching protocol; incorrect prognostic factors - none matching protocol.
Bhattacharyya 2013[22]	Incorrect study design - narrative review.
Blitz 1998[23]	Incorrect prognostic factors - none on exercise/stress testing; insufficient reporting - no multivariate results reported though it was performed
Bonow 1980[24]	Incorrect population - symptomatic severe AR
Bonow 1982[26]	Incorrect study design - narrative review.
Bonow 1983[27]	Incorrect prognostic factors - none matching protocol; incorrect analysis - no multivariate effect sizes reported
Bonow 1985[25]	Incorrect prognostic factors - none matching protocol; incorrect analysis - no multivariate effect sizes reported
Booher 2011[28]	Incorrect study design - narrative review.
Borer 1998[29]	Incorrect prognostic factors - none matching protocol
Borer 2018[30]	Incorrect prognostic factors - none matching protocol
Broch 2016[31]	Incorrect outcomes - none matching protocol; incorrect prognostic factors - measured at baseline rather than on stress/exercise
Carabello 1980[33]	Incorrect population - symptomatic severe AS

Reference	Reason for exclusion
Castillo-Moreno 2016[34]	Incorrect prognostic factors - none matching protocol
Catala 2019[35]	Incorrect prognostic factors - none matching protocol
Cheriex 1994[37]	Incorrect outcomes - none matching protocol; incorrect population - severity and symptomatic status unclear
Chirio 2007[38]	Incorrect analysis - no prognostic effect sizes reported
Cho 2013[39]	Incorrect prognostic factors - none matching protocol
Churchwell 1994[40]	Incorrect study design - narrative review.
Cieslikowski 2007[41]	Incorrect study design - no mention of quality assessment, unclear if individual studies performed MV analysis; insufficient reporting - no OR/RR given for different prognostic factors
Clavel 2008[45]	Incorrect prognostic factors - none matching protocol
Clavel 2010[42]	Incorrect prognostic factors - none matching protocol
Clavel 2012[43]	Incorrect prognostic factors - none on exercise/stress testing
Clavel 2013[44]	Incorrect prognostic factors - none matching protocol
Clavel 2014[47]	Incorrect prognostic factors - none measured on exercise/stress testing
Clavel 2014[48]	Incorrect study design - narrative review.
Clavel 2016[46]	Incorrect study design - narrative review.
Coisne 2015[49]	Incorrect outcomes - none matching protocol; incorrect population - majority severe symptomatic
Cristina de Castro Faria 2020[50]	Incorrect population - majority with previous valve intervention; incorrect prognostic factors - none matching protocol
de Abreu 2017[52]	Incorrect population - not diagnosed valve disease, but known or suspected coronary artery disease
de Arenaza 2010[53]	Incorrect prognostic factors - none matching protocol
deFilippi 1995[54]	Incorrect study design - no prognostic effect sizes reported; incorrect population - symptomatic severe AS
Dehghani 2020[55]	Incorrect investigations: cardiac catheterisation not stress testing
Dhoble 2014[56]	Insufficient controlling for confounding
Ding 2008[57]	Incorrect population - symptomatic severe AS; incorrect prognostic factors - none on stress/exercise testing.
Dobarro 2020[58]	Incorrect prognostic factors - none matching protocol; insufficient analysis - no formal prognostic analysis performed.
Domanski 2017[59]	Incorrect study design - abstract only
Dominguez-Rodriguez 2014[60]	Incorrect prognostic factors - none matching protocol
Donal 2011[62]	Incorrect prognostic factors - none matching protocol; incorrect outcomes - none matching protocol
Donal 2012[61]	Incorrect population - majority symptomatic, severe MR; incorrect prognostic factors - none matching protocol; incorrect analysis - no prognostic effect sizes reported
El Zayat 2015[63]	Incorrect prognostic factors - none matching protocol
Ennezat 2008[64]	Incorrect prognostic factors - none matching protocol
Ennezat 2009[65]	Incorrect study design - narrative review
Ettinger 1972[66]	Incorrect study design - no prognostic effect sizes reported
Ewe 2015[67]	Incorrect prognostic factors - none measured on exercise/stress testing

Reference	Reason for exclusion
Ferrer-Sistach 2020[68]	Incorrect study design - no prognostic analysis
Flett 2012[69]	Incorrect prognostic factors - none measured on exercise/stress testing
Flint 2020[70]	Incorrect study design - narrative review
Forsberg 2014[71]	Incorrect analysis - no prognostic effect sizes reported
Garbi 2015[73]	Incorrect study design - guide on exercise testing based on evidence and guidelines
Gee 1985[74]	Incorrect analysis - no prognostic effect sizes reported
Gentry 2019[76]	Incorrect population - large proportion with previous mitral valve intervention; incorrect prognostic factors - none matching protocol
Gentry Iii 2017[75]	Incorrect study design - narrative review
Goublaire 2018[77]	Incorrect prognostic factors - though some matching protocol are mentioned, does not give results for these in non-continuous format
Green 2013[78]	Incorrect population - severe symptomatic AS; incorrect prognostic factors - none matching protocol
Grigioni 2018[79]	Incorrect prognostic factors - none on exercise/stress testing
Grimaldi 2012[80]	Incorrect analysis - no prognostic effect sizes reported; incorrect study design - no follow-up of outcomes
Hachicha 2007[81]	Incorrect prognostic factors - none measured on exercise/stress testing
Hayek 2015[82]	Incorrect prognostic factors - none matching protocol
Helin 2010[83]	Incorrect study design - no follow-up of patient outcomes; incorrect analysis - no prognostic effect sizes reported
Henri 2014[86]	Incorrect study design - narrative review
Henri 2014[84]	Incorrect study design - narrative review
Henri 2014[85]	Incorrect outcomes - none matching protocol
Herrmann 2013[87]	Incorrect prognostic factors - none measured on exercise/stress testing
Hirasawa 2020[88]	Incorrect prognostic factors - none matching protocol
Ho 2020[89]	Incorrect population - not diagnosed valve disease, only a small proportion had valve disease
Holland 2010[90]	Incorrect population - not limited to those with diagnosed valve disease
Huded 2018[91]	Incorrect prognostic factors - none matching protocol
Hwang 2020[92]	Incorrect prognostic factors and outcomes – none matching protocol
Izumo 2016[93]	Incorrect study design - narrative review
Izumo 2020[94]	Incorrect prognostic factors - none matching protocol
Jakrapanichakul 1996[95]	Incorrect outcomes - none matching protocol; incorrect analysis - no prognostic effect sizes reported
Jukl 2018[96]	Full text not in English
Kaleschke 2011[97]	Incorrect study design - narrative review.
Kamijima 2017[98]	Incorrect analysis - no prognostic effect sizes reported for outcomes matching the protocol
Kamimura 2016[99]	Incorrect prognostic factors - none matching protocol; incorrect population - mixed AS severity and unclear symptomatic status
Karaian 1985[100]	Incorrect prognostic factors - none matching protocol; incorrect outcomes - none matching protocol
Kasegawa 1990[101]	Incorrect analysis - no prognostic effect sizes reported for outcomes matching the protocol
Kefer 2013[102]	Incorrect population - symptomatic severe AS; incorrect prognostic factors - none measured on exercise/stress testing

Reference	Reason for exclusion
Kellermair 2020[103]	Incorrect outcomes - none matching protocol; incorrect analysis - no prognostic effect sizes reported
Kessler 2019[104]	Incorrect population - symptomatic severe MR
Khattar 2019[105]	Incorrect study design - narrative review.
Kim 2003[107]	Incorrect analysis - no prognostic effect sizes reported; incorrect population - majority are severe symptomatic valve disease
Kim 2008[108]	Incorrect prognostic factors - none matching protocol
Kim 2018[109]	Incorrect prognostic factors - none measured on exercise/stress testing
Kim 2020[106]	Incorrect prognostic factors - none matching protocol
Kinnaird 2003[110]	Incorrect analysis - no prognostic effect sizes reported
Kitai 2020[111]	Incorrect study design - narrative review.
Klues 1997[112]	Incorrect analysis - no prognostic analysis; incorrect study design - no follow-up of patient outcomes
Kokkinidis 2018[113]	Incorrect population - symptomatic severe AS; incorrect prognostic factors - none measured on exercise/stress
Kusljugic 2010[114]	Incorrect analysis - no prognostic effect sizes reported
Kusljugic 2014[115]	Conference abstract only – insufficient data
Kusunose 2013[118]	Incorrect prognostic factors - none matching protocol
Kusunose 2014[117]	Incorrect prognostic factors - none matching protocol
Kusunose 2017[119]	Incorrect prognostic factors - none matching protocol
Kusunose 2020[116]	Incorrect study design - narrative review.
Lafitte 2009[120]	Incorrect prognostic factors - none matching protocol; incorrect analysis - no prognostic effect sizes reported
Lancellotti 2003[133]	Incorrect analysis - no prognostic effect sizes reported
Lancellotti 2005[125]	Insufficient reporting - no prognostic effect sizes reported
Lancellotti 2008[121]	Incorrect prognostic factors - none matching protocol; incorrect analysis - no prognostic effect sizes reported
Lancellotti 2012[127]	Incorrect study design - narrative review.
Lancellotti 2012[129]	Incorrect prognostic factors - none matching protocol
Lancellotti 2012[128]	Incorrect prognostic factors - none measured on exercise/stress testing
Lancellotti 2013[126]	Incorrect study design - narrative review.
Lancellotti 2013[131]	Incorrect study design - narrative review.
Lancellotti 2015[130]	incorrect prognostic factors - none matching protocol
Lancellotti 2018[123]	Incorrect study design - narrative review.
Lange 2006[134]	Incorrect study design - narrative review.
Le 2016[135]	Incorrect outcomes - none matching protocol
Le 2017[136]	Insufficient controlling for confounders
Le 2017[137]	Insufficient reporting - prognostic results for factors matching protocol not reported
Ledwoch 2018[138]	Incorrect population - majority severe, symptomatic MR; incorrect prognostic factors - none matching protocol
Lee 2005[139]	Incorrect analysis - no prognostic effect sizes for outcomes matching protocol
Lee 2012[140]	Incorrect prognostic factors - none measured on exercise/stress testing; incorrect outcomes - none matching the protocol.
Lee 2019[141]	Incorrect analysis - no prognostic effect sizes reported
Leung 1996[144]	Incorrect prognostic factors - none matching protocol

Reference	Reason for exclusion
Leung 1997[143]	Incorrect prognostic factors - none measured on exercise/stress testing
Leung 1999[142]	Incorrect prognostic factors - none matching protocol; incorrect analysis - no prognostic analysis
Levy 2008[147]	Incorrect prognostic factors - none matching protocol
Levy 2011[148]	incorrect prognostic factors - none matching protocol
Levy 2014[146]	Incorrect prognostic factors - none matching protocol
Levy-Neuman 2019[145]	Insufficient controlling for confounders
Lindman 2015[149]	Incorrect prognostic factors - none measured on exercise/stress testing; incorrect population - majority symptomatic severe AS
Lindsay 1987[150]	Incorrect prognostic factors - none matching protocol; incorrect analysis - no prognostic analysis
Maes 2019[151]	Incorrect prognostic factors - none matching protocol
Magne 2010[154]	Incorrect analysis - no prognostic effect sizes reported
Magne 2012[158]	Incorrect prognostic factors - none matching protocol
Magne 2014[156]	Incorrect study design - narrative review.
Magne 2011[153]	Insufficient controlling for confounders
Marechaux 2007[159]	Insufficient controlling for confounders
Marko 2014[161]	Incorrect prognostic factors - none matching protocol
Martinez 2016[162]	Incorrect study design - narrative review.
Masri 2016[163]	Insufficient controlling for confounders
Matsuzoe 2017[164]	Incorrect population - symptomatic severe AS
Mentias 2016[165]	Incorrect prognostic factors - none matching protocol
Mok 2013[167]	Incorrect population - severe symptomatic AS; incorrect prognostic factors - none matching protocol
Monin 2001[169]	Incorrect prognostic factors - none matching protocol
Monin 2003[170]	Incorrect prognostic factors - none matching protocol
Monin 2009[168]	Incorrect prognostic factors - none measured on exercise/stress testing
Moura 2009[172]	Incorrect study design - narrative review.
Murphy 2019[173]	Incorrect prognostic factors - none matching protocol
Naji 2014[175]	Insufficient controlling for confounders
Naji 2014[176]	Incorrect prognostic factors - none matching protocol
Naji 2015[174]	Incorrect prognostic factors - none matching protocol
Naji 2015[177]	Incorrect study design - narrative review.
Niemela 1983[180]	Incorrect outcomes - none matching protocol; incorrect analysis - no multivariate analysis performed
Nishi 2019[181]	Incorrect prognostic factors - none matching protocol
Nishimura 2002[182]	Incorrect analysis - no prognostic effect sizes reported
Noack 2017[183]	Incorrect prognostic factors - none measured on exercise/stress testing
Nylander 1986[184]	Incorrect study design - no prognostic analysis
O'Connor 2010[185]	Incorrect study design - narrative review.
O'Connor 2010[186]	Incorrect study design - narrative review.
Olaf 2012[187]	Incorrect analysis - no prognostic effect sizes reported
Orta Kilickesmez 2013[188]	Incorrect study design - narrative review.

Reference	Reason for exclusion
Orwat 2013[189]	Incorrect study design - narrative review.
Otto 1997[190]	Incorrect prognostic factors - none matching protocol
Ozaki 1999[191]	Incorrect analysis - no prognostic effect sizes reported; incorrect study design - no follow-up of patient outcomes
Park 2013[193]	Incorrect analysis - no prognostic analysis performed for outcomes relevant to the protocol
Park 2017[192]	Insufficient reporting - insufficient information provided for prognostic results
Paul 2004[194]	Incorrect study design - narrative review.
Percy 1993[196]	Incorrect analysis - no prognostic effect sizes reported
Peteiro 2019[197]	Incorrect population - those with dyspnea, not limited to those with valve disease
Petracca 2009[198]	Incorrect analysis - no prognostic effect sizes reported; incorrect study design - no follow-up of patient outcomes
Piatkowski 2020[199]	Incorrect outcomes - none matching protocol; incorrect analysis - no prognostic effect sizes reported
Pibarot 2012[200]	Incorrect study design - narrative review.
Pierard 2007[202]	Incorrect study design - narrative review.
Pierard 2017[201]	Incorrect study design - narrative review.
Plonska-Gosciniak 2020[203]	Incorrect study design - narrative review.
Postolache 2020[205]	Incorrect study design - narrative review.
Procopio 2020[206]	Incorrect study design - diagnostic
Quere 2006[207]	Incorrect prognostic factors - none matching protocol; insufficient reporting - results for multivariate analysis not fully reported
Rafique 2009[208]	Incorrect prognostic factors -definition of abnormal result varied across studies and were combined while they are separate in the protocol; incorrect analysis - unclear if multivariate analysis performed in individual studies.
Raissi 2018[209]	Incorrect study design - narrative review.
Rassi 2013[210]	Incorrect prognostic factors - none matching protocol
Redfors 2017[211]	Incorrect study design - narrative review.
Reis 2004[212]	Incorrect prognostic factors - none matching protocol; incorrect population - any severity and symptomatic status included, and 58% had prior mitral valve intervention.
Ribeiro 2018[213]	Incorrect prognostic factors - none matching protocol
Rimington 2010[214]	Incorrect prognostic factors - none matching protocol; incorrect analysis - no prognostic effect sizes reported for outcomes relevant to protocol
Sade 2009[215]	Incorrect prognostic factors - none matching protocol
Saeed 2018[217]	Insufficient controlling for confounding
Saeed 2020[218]	Incorrect prognostic factors - none matching protocol
Saeed 2020[216]	Incorrect prognostic factors - none matching protocol
Saji 2018[219]	Incorrect prognostic factors - none matching protocol
Saji 2019[220]	Incorrect prognostic factors - none matching protocol
Sathyamurthy 2016[221]	Incorrect study design - narrative review.
Sato 2017[223]	Insufficient controlling for confounding
Sato 2019[222]	Incorrect prognostic factors - none matching protocol
Schulz 2012[225]	Incorrect analysis - no prognostic effect sizes reported

Reference	Reason for exclusion
Schulz 2015[224]	Incorrect prognostic factors - none matching protocol
Sharma 2011[228]	Incorrect prognostic factors - none matching protocol; incorrect analysis - no prognostic effect sizes reported
Sharma 2015[226]	Insufficient controlling for confounding
Sharma 2016[227]	Incorrect study design - no follow-up of patient outcomes and no prognostic analysis
Siemienczuk 1989[229]	Incorrect prognostic factors - none matching protocol; incorrect analysis - no prognostic effect sizes reported
Sinha 2016[232]	Incorrect prognostic factors - none matching protocol; incorrect analysis - no multivariate analysis
Subramanian 2008[233]	Incorrect study design - narrative summary
Sugimoto 2020[234]	Incorrect analysis - no prognostic effect sizes reported; incorrect study design - no follow-up of patient outcomes
Supino 2005[235]	Incorrect prognostic factors - none matching protocol
Supino 2007[236]	Insufficient controlling for confounding
Supino 2013[237]	Incorrect prognostic factors - none matching protocol
Suzuki 2015[238]	Incorrect analysis - no prognostic analysis performed for outcomes relevant to the protocol
Suzuki 2019[239]	Incorrect prognostic factors - none matching protocol
Takeda 2001[240]	Incorrect prognostic factors - none measured on exercise/stress testing
Tam 1999[241]	Incorrect prognostic factors - none matching protocol; incorrect outcomes - none matching protocol
Tamas 2009[242]	Incorrect prognostic factors and outcomes
Tarasoutchi 1999[243]	Incorrect analysis - no prognostic effect sizes reported
Tarasoutchi 2003[244]	Incorrect analysis - no prognostic effect sizes reported for prognostic factors matching protocol
Tarro Genta 2019[245]	Incorrect prognostic factors - none matching protocol
Thompson 1982[246]	Incorrect study design - no follow-up of patient outcomes and no prognostic analysis
Tribouilloy 2009[247]	Incorrect prognostic factors - none measured on exercise/stress testing
Van Pelt 2007[248]	Incorrect study design - no follow-up of patient outcomes and no prognostic analysis
van Zalen 2019[249]	Insufficient accounting for confounding
Vecera 2014[250]	Incorrect prognostic factors - none matching protocol
Velu 2019[251]	Incorrect prognostic factors - none matching protocol; incorrect analysis - no prognostic effect sizes reported
Vitale 2018[252]	Incorrect prognostic factors - none matching protocol
Vitel 2018[253]	Incorrect prognostic factors - none matching protocol
Wahi 2000[254]	Incorrect analysis - no prognostic effect sizes reported
Wang 2014[255]	Incorrect prognostic factors - none measured on exercise/stress testing
Wang 2016[256]	Incorrect prognostic factors - none measured on exercise/stress testing
Weisenberg 2008[257]	Incorrect analysis - no prognostic effect sizes reported
Yousof 1986[258]	Incorrect analysis - no prognostic effect sizes reported
Zuppiroli 2003[259]	Incorrect prognostic factors - none matching protocol

Health Economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2004 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

None.

Appendix K – Research recommendations – full details

K.1 Research recommendation

What is the prognostic value of parameters observed on exercise stress testing and exercise stress echocardiography in asymptomatic severe aortic regurgitation?

K.2 Why this is important

This will inform NICE around the surgical management of patients with asymptomatic aortic regurgitation.

K.3 Rationale for research recommendation

Importance to 'patients' or the population	This would mean another test for a patient and they may get earlier surgery to maintain health. This test is a functional assessment to aid timing of surgery.
Relevance to NICE guidance	The prognostic value of various factors observed on exercise stress testing and exercise stress echocardiography in those that had asymptomatic severe aortic regurgitation at rest was considered in this guideline; however, no studies were identified covering this population. Therefore, no recommendations were made in terms of indicators for intervention observed on exercise testing or echocardiography for this population. Answering this question may provide evidence to be able determine whether any of the listed prognostic factors may be associated with outcome and be an indication for intervention in patients with asymptomatic severe aortic regurgitation at rest.
Relevance to the NHS	This will inform NICE around the surgical management of these patients and some patients may have earlier surgery.
National priorities	Not known
Current evidence base	No studies with appropriate adjustment for confounders were included in the review covering the asymptomatic severe aortic regurgitation population. There was therefore no evidence included that could be used to make recommendations concerning indicators for intervention on exercise testing or echocardiography for this population. Studies providing evidence for the prognostic value of parameters observed on exercise testing or echocardiography in the asymptomatic severe aortic regurgitation population may provide evidence to be able to identify some factors that may be associated with worse outcome and therefore be an indication for intervention.
Equality considerations	None known

K.1.4 Modified PICO table

2

Population	Inclusion Adults aged 18 years and over with diagnosed aortic regurgitation that is asymptomatic and severe at rest and requiring further tests after echocardiography to determine if intervention is needed Exclusion • Children (aged <18 years) • Adults with congenital heart disease (other than bicuspid aortic valves) • Adults with previous intervention for HVD (surgical or transcatheter) • Adults with acute heart failure
Prognostic factor	Exercise stress testing: • Exercise capacity <60% predicted workload for gender, age and weight • Symptoms unmasked in response to exercise • Increase in BNP levels on exercise compared with baseline Exercise stress echocardiography: • Lack of demonstrated contractile reserve at low workload exercise • Decrease in LVEF on exercise compared with baseline • Reduced left ventricular systolic function based on global longitudinal strain on exercise compared with baseline
Comparator	Exercise stress testing: • Exercise capacity ≥60% predicted workload for gender, age and weight • Symptoms not unmasked in response to exercise • No increase in BNP levels on exercise compared with baseline Exercise stress echocardiography: • Presence of demonstrated contractile reserve at low workload exercise • No decrease in LVEF on exercise compared with baseline • No reduction in left ventricular systolic function based on global longitudinal strain on exercise compared with baseline Note that each comparator matches the respective prognostic factor listed above.
Outcome	Indication for intervention based on prognosis for the following without intervention: • Mortality (1 and 5 years)

	• Hospital attendance/admission for heart failure or unplanned intervention (1 and 5 years) • Reduced cardiac function (echo or CMR parameters – for example LVEF <60%) (1 and 5 years) • Symptom onset (1 and 5 years) <u>Indication for intervention based on predictors of the following post-operative outcomes:</u> • Mortality (6 and 12 months) • Hospital attendance for heart failure (6 and 12 months) • Cardiac event-free survival • Reduced cardiac function (echo or CMR parameters – for example LVEF <50%) (6 and 12 months)
Study design	Non-randomised cohort study with adjustment or matching for the following confounders: • Coronary disease • Comorbid lung disease or respiratory insufficiency • Peripheral vascular disease • Arthritis
Timeframe	Long term
Additional information	None

K.125 Research recommendation

What is the prognostic value of severe mitral regurgitation unmasked on exercise echocardiography in adults with symptomatic non-severe mitral regurgitation at rest?

K.126 Why this is important

This will inform NICE around the timing of surgery for patients with symptomatic non-severe mitral regurgitation.

K.127 Rationale for research recommendation

Importance to 'patients' or the population	This will be another test that may give a clear cause of the patient's symptoms and if due to the mitral regurgitation, mitral valve surgery will make an improvement to symptoms.
Relevance to NICE guidance	The prognostic value of unmasking severe mitral regurgitation on exercise echocardiography in those that were symptomatic but non-severe at rest was considered in this guideline; however, only one study was identified and used as indirect evidence for this prognostic factor. This was not considered to be sufficient evidence to make a recommendation for this prognostic factor in terms of whether or not intervention is

	indicated if severe mitral regurgitation is unmasked on exercise echocardiography in these patients. Answering this question would provide more robust evidence to determine whether the unmasking of severe status on exercise echocardiography should be an indication for intervention in patients with symptomatic non-severe mitral regurgitation at rest.
Relevance to the NHS	There will be more tests performed and some patients will be referred for earlier surgery. However patients will be better managed.
National priorities	Not known
Current evidence base	Although one study was included in the evidence review as indirect evidence for the prognostic value of severe status being unmasked on exercise echocardiography in those with symptomatic non-severe mitral regurgitation at rest, this study was limited as it included mild-severe patients, with 32% already having symptomatic severe mitral regurgitation at rest, and the prognostic factor was an increase in effective regurgitant orifice area ≥13 mm^2 on exercise. The prognostic factor did not represent an unmasking of severe disease in all patients as a proportion already had severe disease at rest and it was unclear whether the increase of 13 mm^2 would represent the unmasking of severe disease in all non-severe patients at rest, particularly those with mild disease at rest. There was therefore not considered to be evidence to support the inclusion of unmasking of severe disease on exercise echocardiography as an indication for intervention in those with symptomatic non-severe mitral regurgitation at rest. Studies providing direct evidence for this prognostic factor in the symptomatic non-severe mitral regurgitation population may provide evidence to be able to determine whether this observation on exercise echocardiography should be an indication for intervention in this population.
Equality considerations	None known

1

K.12.8 Modified PICO table

3

Population	<u>Inclusion</u> Adults aged 18 years and over with diagnosed mitral regurgitation that is symptomatic and non-severe at rest and requiring further tests after echocardiography to determine if intervention is needed <u>Exclusion</u> • Children (aged <18 years)

	• Adults with congenital heart disease (other than bicuspid aortic valves) • Adults with previous intervention for HVD (surgical or transcatheter) • Adults with acute heart failure
Prognostic factor	Severe mitral regurgitation revealed on exercise echocardiography
Comparator	Non-severe mitral regurgitation on exercise echocardiography
Outcome	<u>Indication for intervention based on prognosis for the following without intervention:</u> • Mortality (1 and 5 years) • Hospital attendance/admission for heart failure or unplanned intervention (1 and 5 years) • Reduced cardiac function (echo or CMR parameters – for example LVEF <60%) (1 and 5 years) <u>Indication for intervention based on predictors of the following post-operative outcomes:</u> • Mortality (6 and 12 months) • Hospital attendance for heart failure (6 and 12 months) • Cardiac event-free survival • Reduced cardiac function (echo or CMR parameters – for example LVEF <50%) (6 and 12 months)
Study design	Non-randomised cohort study with adjustment or matching for the following confounders: • Coronary disease • Comorbid lung disease or respiratory insufficiency • Peripheral vascular disease • Arthritis
Timeframe	Long term
Additional information	None