National Institute for Health and Care Excellence

Draft

Heart valve disease presenting in adults: investigation and management

[D] Evidence review for indications for intervention

NICE guideline

Prognostic evidence review underpinning recommendations 1.3.2, 1.3.7, 1.3.8 and research recommendations in the NICE guideline

March 2021

Draft for consultation

Developed by the National Guideline Centre, hosted by the Royal College of Physicians

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and, where appropriate, their carer or guardian.

Local commissioners and providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

ISBN
[tba]

Contents

1 Indications for intervention in asymptomatic severe heart valve disease

1.1 Review question: What are the indications that interventions should be offered to adults with asymptomatic, severe heart valve disease?

1.2 Introduction

Heart valve disease is a progressive condition, with gradual worsening, developing clinical and haemodynamic consequences usually late in the course of the disease. Characterisation of heart valve disease as severe based on imaging parameters, corresponds to a degree of valve function abnormality that is compatible with significant haemodynamic consequences and/or the development of symptoms, and that may require valve intervention. Nevertheless, solely reaching the thresholds defining the heart valve disease as severe, does not usually suffice to indicate intervention, particularly as many patients cope with their severe valve disease well, and the intervention (usually cardiac surgery) carries significant morbidity and a small mortality risk. Valve intervention is indicated when the expected benefit surpasses the risk of the procedure, and this generally occurs at the onset of cardiac decompensation.

It is generally agreed that patients with severe heart valve disease and symptoms should be offered valve intervention. However, even in the absence of symptoms, severe heart valve disease may require intervention when heart valve disease parameters or haemodynamic consequences are demonstrated to be associated with a worse prognosis if we wait for symptoms to occur. Consequently, it is important to determine the indications for intervention in asymptomatic severe heart valve disease.

1.3 PICO table

For full details see the review protocol in Appendix A:.

Table 1: PICO characteristics of review question

Population	Adults aged 18 years and over with diagnosed severe heart valve disease that is asymptomatic, stratified by the type of heart valve disease as follows: • aortic [including bicuspid] stenosis • aortic regurgitation • mitral stenosis • mitral regurgitation • tricuspid regurgitation

Prognostic variables under consideration	**1. Mitral regurgitation**
	Primary mitral regurgitation
	• left ventricular systolic function based on ejection fraction <50% or <60%
	• Left ventricular systolic function based on global longitudinal strain (absolute value <20%; may be reported as in the range 0 to -20% or >-20%)
	• left ventricular end systolic diameter ≥40mm or ≥45mm
	• peak systolic pulmonary artery pressure >50mmHg
	• left atrial dimensions (volume / volume index) ≥60 mL/m^2 BSA
	• Repairability/valve morphology:
	  ○ posterior leaflet prolapse,
	  ○ anterior leaflet prolapse,

	○ bileaflet prolapse ○ flail valve / ruptured chordae • development of atrial fibrillation • BNP increase at serial measurements (without other explanation) **2. Aortic stenosis** • Peak velocity >5m/sec or >5.5m/sec • Rate of progression of velocity >0.3m/sec/year • Aortic valve area <0.6cm^2 • left ventricular systolic function based on ejection fraction <50% or <60% • left ventricular systolic function based on global longitudinal strain absolute value <20%; may be reported as 0 to -20% or >-20%) • parameters of diastolic function / indicators of left atrial filling pressure (E/e'>14) • systolic pulmonary artery pressure >60mmHg (without other explanation) • BNP increase at serial measurements (without other explanation) **3. Aortic regurgitation** • left ventricular systolic function based on ejection fraction <50% • left ventricular systolic function based on global longitudinal strain absolute value <20%; may be reported as 0 to -20% or >-20%) • left ventricular dimensions ○ end diastolic diameter, LVEDD >70mm ○ end systolic diameter, LVESD >50mm ○ end diastolic volume, LVEDV >25mm/m^2 BSA • BNP increase at serial measurements (without other explanation) **4. Mitral stenosis** • mitral valve area <1cm^2 or <1.5cm^2 • systolic pulmonary artery pressure >50mmHg • mitral valve gradient mean gradient >5mmHg at rest • reduced right ventricular function (tricuspid annular plane systolic excursion [TAPSE] <17) • mitral valve morphology – deemed suitable for transcatheter balloon valvotomy • BNP increase at serial measurements (without other explanation) **5. Tricuspid regurgitation (isolated)** • reduced right ventricular systolic function – no thresholds • increasing right ventricular dimensions – no thresholds (dilated – mild, moderate, severe) • BNP increase at serial measurements (without other explanation) • Valve morphology – suitable for repair If studies report combinations of these factors these will be included
Confounding factors	• Risk scores (e.g. EuroScore I or II, STS score) ○ Age ○ Sex ○ Renal impairment ○ Extra cardiac arteriopathy/ Peripheral arterial disease/ Cerebrovascular disease ○ Previous cardiac surgery

	○ Chronic lung disease ○ Diabetes ○ Hypertension ○ Prior MI ○ Active endocarditis • Frailty scores (e.g. CSHA, Katz score)
Outcomes	Indication for intervention based on prognosis for the following without intervention: • Mortality (≥12 months) • Hospital admission for heart failure (≥12 months) • Reduced cardiac function (echo parameters – LVEF) Indication for intervention based on pre-operative predictors of the following post-operative outcomes: • Mortality (≥12 months) • Hospital admission for heart failure (≥12 months)
Study design	• Prospective and retrospective cohort studies • Systematic reviews of the above

1.4 Clinical evidence

1.4.1 Included studies

A search was conducted for prospective and retrospective cohort studies investigating the association of various prognostic factors measured on echocardiography or clinical assessment and outcomes in those that received conservative management of valve disease and those that received intervention for valve disease. The prognostic factors were different depending on the type (e.g. aortic regurgitation or aortic stenosis) of valve disease and full details are provided in the protocol.

Twenty nine studies were included in the review;[6, 26, 30, 39, 51, 56, 59, 64, 107, 121, 125, 131, 135, 140, 156, 158, 166, 179, 187, 188, 208, 209, 219, 223, 229, 244, 253, 276, 281] these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summaries below (Table 3 to Table 19).

Some studies reported more than one prognostic factor and/or threshold, and the available evidence covered the following populations and prognostic factors:

- Aortic stenosis
  - Peak aortic jet velocity (Vmax): 9 studies[30, 125, 140, 188, 219, 223, 229, 244, 281]
  - Aortic valve area (AVA): 4 studies[121, 166, 223, 229]
  - Left ventricular ejection fraction (LVEF): 5 studies[26, 39, 140, 179, 244]
  - Left ventricular global longitudinal strain (LV-GLS): 1 individual-patient data (IPD) meta-analysis of 10 original studies[158], and one additional study[253]
  - B-type natriuretic peptide (BNP): 3 studies[56, 107, 187]
  - Composite indicators: 1 study[131]
- Aortic regurgitation
  - LVEF: 1 study[64]
  - Left ventricular dimensions: 3 studies[64, 156, 209]
  - BNP: 1 study[209]
- Mitral regurgitation
  - LVEF: 1 study[51]

- Left ventricular end systolic diameter (LVESD): 2 studies[135, 208]
- Left atrial volume index (LAVI): 1 study[6]
- Repairability/valve morphology: 2 studies[59, 135]
- Atrial fibrillation: 2 studies[59, 276]
- BNP: 1 study[208]

Outcomes from the IPD meta-analysis were included as reported in the study. This was based on individual participant data gained from the study authors of 10 original studies of unique patient cohorts and was adjusted for age, gender, AVAi, and LVEF. One further study of LV-GLS in aortic stenosis published after this meta-analysis was included in this review but not combined with the IPD meta-analysis findings.

No relevant clinical studies investigating the effects of any of the relevant pre-specified prognostic factors were identified for the following populations:

- Mitral stenosis
- Tricuspid regurgitation

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 included, but they were downgraded for indirectness. This was because there was limited available evidence that had accounted for any 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 only reported univariate results were excluded.

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

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

1.4.2 Excluded studies

See the excluded studies list in Appendix I:.

1.4.8 Summary of clinical studies included in the evidence review

2 **Table 2: Summary of studies included in the evidence review**

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
Aortic stenosis						
Bohbot 2017[30]	Severe AS and preserved LVEF. Subgroup for those that were minimally symptomatic or asymptomatic described. N=558 Prospectively identified and included in an electronic database from 2 French university hospital echo labs	Multivariable Cox proportional hazards model.	**Vmax**: 4-4.49 m/s n=229 (referent) 4.50-4.99 m/s n=160 5-5.49 m/s n=104 ≥5.5 m/s n=65 <5.0m/s n=389 (referent) ≥5.0 m/s n=169	Age, sex, BSA, hypertension, New York Heart Association class, coronary artery disease, history of atrial fibrillation, comorbidity index, LVEF, and aortic valve surgery (treated as a time-dependent covariate).	All-cause mortality Median (IQR) follow-up was 38.0 (6–190) months.	NYHA class 1 and 2 (No or minimal symptoms: atypical chest pain and elderly patients with minimal dyspnoea not clearly related to AS were considered to be minimally symptomatic). >80% of total population had AVR during follow-up
Bohbot 2019[26]	Severe AS with no or minimal symptoms, some managed surgically others medically N=1678 Prospectively identified from electronic database of 2	Multivariable Cox proportional hazards model.	LVEF ≥60% (referent) LVEF <60% n = 570 LVEF ≥55% (referent) LVEF <55% n = 239	Age, sex, body surface area, hypertension, coronary artery disease, history of myocardial infarction, history of atrial fibrillation, comorbidity index, and aortic valve area.	All-cause mortality Median (IQR) follow-up was 38.0 (19–76) months.	Asymptomatic and minimal symptoms - proportion unclear. No or minimal symptoms: atypical chest pain and elderly patients with minimal dyspnoea not clearly related to AS were considered to be minimally symptomatic.

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
	French and 1 Belgian tertiary centres					Initially 45% were medically managed and 55% surgically managed Mortality could have been pre- or post-surgery
Campo 2019[39]	Asymptomatic severe AS who had surgery recommended N=104 Sourced from a single tertiary centre	Multivariable Cox proportional hazards model.	LVEF >50% LVEF ≤50% (referent)	AVR, age, sex, mean gradient, EF, coronary artery disease	All-cause mortality Average follow-up unclear. Survival curves calculated up to 5 years follow-up	Threshold not pre-specified and differs between cohorts Mortality could have been pre- or post-surgery (90% had surgery by 1 year)
Clavel 2014[56]	Asymptomatic severe AS N=565	Multivariable Cox proportional hazards model.	Activated BNP Activated BNP <2 times normal Activated BNP 2 to 3 times normal Activated BNP ≥3 times normal Normal BNP level (referent)	Age, sex, body surface area, atrial fibrillation, Charlson score index, symptoms, creatinine level, haemoglobin level, systolic blood pressure, indexed aortic valve area, indexed stroke volume, and LV ejection fraction. Further adjusted for aortic valve replacement as a time-dependent variable	All-cause mortality Mean follow-up of 4.3 (2.4) years Survival curves available up to 8 years follow-up	Number in the severe asymptomatic subgroup unknown 265 had AVR during follow-up Mortality could have been pre- or post-surgery
Henri 2016[107]	Asymptomatic aortic stenosis of at least moderate	Multivariable Cox proportional hazards model.	Median annualised change in BNP >20pg/ml/year	Variables with a P value <0.10 in univariable were	Adverse cardiac events (symptoms, aortic	Indirect outcome and population:

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
	severity and preserved LVEF N=69 Consecutive sample from a single centre		Median annualised change in BNP ≤20pg/ml/year (referent) BNP level measurement was performed at baseline and repeated after at least 6 months of follow-up, and then, after every 6 or 12 months.	incorporated into the multivariable model. **Included in the model:** age, dyslipidaemia and echocardiographic variables (peak aortic velocity and indexed left atrial area)	valve replacement as indicated by symptoms or LV dysfunction according current class I indication, or cardiovascular death) Mean follow-up of 24 (17) months	Proportion with severe AS unclear (mean baseline Vmax 3.8±0.7 m/s; indexed valve area 0.53±0.13cm/m^2). AVR included in end-point, other outcome components would be pre-operative
Kanamori 2019[121]	Asymptomatic severe AS with normal LVEF managed conservatively. N=1309 Consecutive patients with severe AS enrolled in the CURRENT AS registry of 27 centres in Japan between January 2003 and December 2011	Multivariable Cox proportional hazards model.	AVA >0.80 cm^2, N=645 (referent) 0.8 cm^2 ≥AVA>0.6 cm^2, N=465 AVA ≤0.6 cm^2, N=199	Age, sex, body mass index, hypertension, current smoking, diabetes mellitus on insulin, coronary artery disease, prior myocardial infarction, prior symptomatic stroke, atrial fibrillation or flutter, aorta/peripheral artery disease, serum creatinine, haemodialysis, anaemia, liver cirrhosis, malignancy currently under treatment, chronic lung disease, any valvular disease, LVEF ≥68% and TR	• All-cause mortality • Cardiovascular mortality • Aortic valve-related mortality • Heart failure hospitalisation Median (IQR) follow-up duration of the surviving patients was 1203 (773–1575) days	Indirect threshold comparison Excluded if AVR was the initial strategy; 27% had AVR during follow-up

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
				pressure gradient ≥40 mm Hg		
Kang 2010[125]	Asymptomatic very severe AS - early surgery or conservative treatment N=95 Prospective registry from 1996-2006 including all consecutive patients with AS undergoing echocardiography at multiple sites All study patients regularly visited their physicians at 3- to 6-month intervals	Multivariable Cox proportional hazards model.	AV velocity <5 m/s, n=63 AV velocity ≥5 m/s, n=32	EuroSCORE, unclear if other variables included	Cardiac mortality Median (IQR) follow-up was 1769 (1020–2423) days	Analysis limited to the conservative management group, 46/95 had surgery during follow-up. Mortality includes pre- and post-operative
Kitai 2017[131]	Asymptomatic severe AS with normal LVEF managed conservatively. N=1517 Consecutive patients with severe AS enrolled in the CURRENT AS registry of 27	Multivariable Cox proportional hazards model.	Grouped according to the 2014 ACC/AHA guidelines for surgery: <u>Group 1 (N=122) met the recommendation for surgery:</u> • high-gradient (HG)-AS (Vmax≥4.0m/s or mPG≥40mmHg) with ejection fraction (EF)<50%, n=20 *or* • very HG-AS (Vmax≥5.0m/s or	Age, male, BMI <22 kg/m2, acute heart failure, hypertension, current smoking, diabetes mellitus on insulin therapy, coronary artery disease, past myocardial infarction, past symptomatic stroke, atrial fibrillation or flutter, aortic/peripheral	• All-cause mortality • Cardiovascular mortality • Aortic valve-related mortality • Heart failure hospitalisation • Median follow-up duration 1360 (IQR: 1069-16669) days	Initial conservative management 40% had AVR during follow-up (decision made by individual physicians, no pre-defined strategy); outcomes could have been pre- or post-operative

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
	centres in Japan between January 2003 and December 2011		mPG≥60mmHg) and EF≥50%, n=102 <u>Group 2 (N=1390) did not meet the recommendation for surgery,</u> and was further subdivided into • HG-AS (Vmax≥4.0m/s or mPG≥40mmHg) with preserved EF ≥50% (HGpEF-AS, N=498) • low-gradient (LG)-AS (Vmax <4.0 m/s and mPG <40 mmHg, but AVA<1.0cm^2) (N=892). ○ Preserved EF ≥50% n=789 ○ Reduced EF <50% n=103	vascular disease, haemodialysis, anaemia, liver cirrhosis, malignancy currently under treatment, chronic lung disease, any combined valvular disease and tricuspid regurgitation pressure gradient ≥40 mm Hg.		
Lancellotti 2018[140]	Asymptomatic severe AS N=834 HAVEC Registry data from multiple sites, based on consecutive patients	Multivariable Cox proportional hazards model.	Peak aortic jet velocity >5 LVEF <60%	Age, sex, comorbidities, AS severity, and LVEF	In those without/before AVR: • All-cause mortality • Cardiovascular mortality In those who had AVR: • Post-AVR mortality	22% excluded based on missing data on LVEF or AS severity. 388/861 with severe AS had AVR during follow-up One analysis with patient censored at time of AVR and a second including post-procedural outcomes for those with AVR

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
					Mean (SD; range) follow-up time was 27 (24; 2-224) months for the whole cohort (moderate and severe); not available for the severe subgroup separately	
Magne 2019[158]	Asymptomatic moderate/severe AS (82% severe) N=1067 Individual participant data gained from study authors of 10 original studies of unique patient cohorts	Multivariable Cox proportional hazards model.	LV-GLS >14.7 n=722 LV-GLS ≤14.7 n=345	Age, gender, AVAi, and LVEF	Mortality Median (IQR) follow-up 1.8 (0.9 to 2.8) years	Threshold does not match protocol Unclear if outcomes are with or without surgery
Marechaux 2016[166]	Severe asymptomatic AS treated initially with medical management strategy N=199 Sourced from 2 sites between 2000 and 2012	Multivariable Cox proportional hazards model.	AVA ≤0.6 cm^2, n=39 AVA >0.6 cm^2, n=160	Age, sex, hypertension, coronary artery disease, history of atrial fibrillation, Charlson comorbidity index and left ventricular ejection fraction	All-cause mortality Estimated median follow-up was 48 months (by reverse Kaplan–Meier method)	Mortality included pre- or post-surgery: 112/199 had aortic valve replacement during follow-up

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
Minamino-Muta 2020[179]	Asymptomatic severe AS under watchful waiting N=1274 Consecutive patients with severe AS enrolled in the CURRENT AS registry of 27 centres in Japan between January 2003 and December 2011	Multivariable logistic regression model	LVEF <60%, n=168 LVEF ≥60%, n=648 (referent)	Diabetes mellitus, haemoglobin ≤11.0 g/dL, haemodialysis, chronic lung disease and any concomitant valve disease (moderate or severe). Note that only those variables that reached <0.10 significance level on univariate analysis were considered for entry into the multivariate analysis	AS-related death or heart failure hospitalisation at 1 year	Managed conservatively and reached 1 year follow-up without surgery
Nakatsuma 2017[188]	Severe asymptomatic AS not referred for AVR N=596 Consecutive patients with severe AS enrolled in the CURRENT AS registry of 27 centres in Japan between January 2003 and December 2011	Multivariable Cox proportional hazards model.	4.0 m/s ≤ Vmax <4.5 m/s, n=364 4.5 ≤ Vmax <5.0 m/s, n=140 Vmax ≥5.0 m/s, n=92	Age, male, BMI <22 kg/m2, acute heart failure, hypertension, current smoking, diabetes mellitus on insulin therapy, past myocardial infarction, past symptomatic stroke, atrial fibrillation or flutter, aortic/peripheral vascular disease, haemodialysis, anaemia, liver cirrhosis, malignancy currently under treatment, chronic lung disease, left	• All-cause mortality • Cardiovascular mortality • Aortic valve-related mortality • Heart failure hospitalisation • Median follow-up duration of surviving patients in whole sample population was 1336 (IQR, 966-1817) days. Not reported separately for	Indirect indicator definition: threshold not above and below a certain value Conservatively managed, but >40% had AVR during follow-up

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
				ventricular mass ≥181 g, any combined valvular disease and tricuspid regurgitation pressure gradient ≥40 mm Hg.	the asymptomatic subgroup.	
Nakatsuma 2019[187]	Severe asymptomatic AS not referred for AVR N=387 Consecutive patients with severe AS enrolled in the CURRENT AS registry of 27 centres in Japan between January 2003 and December 2011	Multivariable Cox proportional hazards model.	Group 1: BNP<100 pg/mL, n=201 (referent) Group 2: 100≤BNP<200 pg/mL, n=94 Group 3: 200≤BNP<300 pg/mL, n=42 Group 4: BNP≥300 pg/mL, n=50	Age, male sex, body mass index and the serum creatinine level	Composite of aortic valve-related death or hospitalization due to HF Median follow-up duration 1190 (IQR: 732-1540) days	Conservatively managed
Rosenhek 2000[219]	Asymptomatic severe AS N=128 Prospective cohort study of those in single outpatient clinic for heart valve disease between January and December 1994	Multivariable Cox proportional hazards model.	Aortic jet velocity (Vmax) ≥4.5 m/sec, n=64 Aortic jet velocity (Vmax) <4.5 m/sec, n=62 (referent)	Age, sex, coronary artery disease, hypertension, diabetes, hypercholesterolaemia, degree of aortic valve calcification and aortic jet velocity	Death or aortic valve replacement indication due to the development of symptoms Mean follow-up was 22±18 months (range, 0 to 54 months)	22 patients received AVR within 3 months of initial examination despite remaining asymptomatic (these were censored from the analysis). A further 59 valve replacements were performed during follow-up due to symptom development.

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
						Pre-operative mortality Reported as RR despite methods stating Cox proportional hazards model
Rosenhek 2010[223]	Asymptomatic very severe AS N=116 Prospective cohort study of those in single outpatient clinic for heart valve disease between 1995 and 2008	Multivariable Cox proportional hazards model.	Vmax 5.0 to 5.5 m/s, n=72 (referent) Vmax ≥5.5 m/s, n=44 Aortic valve area <0.6 cm^2, n=47 Aortic valve area ≥0.6 cm^2, n=69 (referent)	Age >70 years, sex, coronary artery disease, hypertension, diabetes mellitus, hypercholesterolaemia, aortic valve area <0.6 cm2, aortic valve peak velocity ≥5.5 m/s were included in the multivariable analysis.	Cardiac mortality or indication for aortic valve replacement Median (IQR) follow-up was 41 (26-63) months	Treated conservatively with watchful waiting: AVR in 79/116 patients during follow-up.
Saito 2012[229]	Severe asymptomatic AS N=103 Sourced from a single site between 2001 and 2007.	Multivariable Cox proportional hazards model.	Aortic valve area index (AVAI) <0.6 cm^2/m^2 Aortic valve area index (AVAI) ≥0.6 cm^2/m^2 (referent) Aortic valve area <0.75 cm^2 Aortic valve area ≥0.75 cm2 (referent) Vmax >4.0 m/s Vmax ≤4.0 m/s (referent)	AVAI <0.6 cm^2/m^2 , aortic valve area <0.75 cm^2 and Vmax >4.0 m/s (Only the three variables with P-values <0.05 on univariate analysis were incorporated into the multivariate model.)	Cardiovascular mortality or aortic valve replacement Mean (SD) follow-up was 36 (27) months	Thresholds used do not match those in our protocol 31/103 underwent aortic valve replacement during the follow-up period.

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
Taniguchi 2018[244]	Asymptomatic severe AS, divided into AVR and conservative management. N=1808 Consecutive patients with severe AS enrolled in the CURRENT AS registry of 27 centres in Japan between January 2003 and December 2011	Multivariable Cox proportional hazards model.	Vmax ≥5 m/s, n=207 Vmax <5 m/s, n=1601 (referent) LVEF <60%, n=355 LVEF ≥60%, n=1453 (referent)	Vmax ≥5 m/s, LVEF <60%, age ≥80 years, male, BMI <22 kg/m2, past myocardial infarction, atrial fibrillation or flutter, haemodialysis, malignancy currently under treatment and any combined valvular disease. Centre was incorporated as a stratification variable.	Sudden death Median follow-up of surviving patients in the entire cohort was 1334 (IQR, 1019-1701) days. Not specified for the asymptomatic subgroup.	Indirect outcome Number receiving aortic valve replacement/surgery during follow-up not reported but censored at time of AVR so outcomes are pre-operative
Thellier 2020[253]	Severe AS with no or mild symptoms and LVEF ≥50% N=332 Retrospective cohort study of consecutive patients at a single hospital from 2011 to 2018.	Multivariable Cox proportional hazards model and propensity matching	LV-GLS ≤15 LV-GLS >15 (referent)	Multivariate model 1: age, sex, Charlson comorbidity index, CAD, hypertension, AF, BMI and AVR as a time-dependent variable. Multivariate model 2: echocardiographic AVA, LVH, LAVi ≥34ml/m^2, sPAP >60 mmHg, E/e' >14, RV dysfunction, LVEF <60% and LV SVi <30 ml/m^2 and AVR	All-cause mortality Median follow-up 42 (IQR: 37-46) months	Threshold used does not match our protocol and includes people with mild AS-related symptoms

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
				as a time-dependent variable. Multivariate model 3: age, sex, Charlson comorbidity index, CAD, hypertension, AF, BMI, AVA, LV SVi <30 ml/m^2, LVEF <60% and AVR as a time-dependent variable. Propensity matching for: age, sex, AF, comorbidity, AVA, LV SVi, LVEF, RV dysfunction.		
Zilberszac 2017[281]	Asymptomatic severe AS aged >70 years n=103 Prospective cohort study of those in single outpatient clinic for heart valve disease between 1999 and 2009	Multivariable Cox proportional hazards model	Vmax ≥5.0 m/s, n=39 4.0 to 5.0 m/s, n=64	Vmax ≥5.0 m/s, aortic valve area (continuous), age (continuous), aortic valve calcification, hypertension, hypercholesterolaemia, diabetes and coronary artery disease	Cardiac mortality or indication for aortic valve replacement Median potential follow-up was 19.4 (IQR, 9.8-36.4) months	Includes both those that would have had intervention and those watchful waiting Aortic valve surgery was performed in 71/103
Aortic regurgitation						
de Meester 2019[64]	Severe AR (subanalysis for asymptomatic)	Multivariable Cox proportional hazards model	LVEF <55% LVEF ≥55% (referent) LVESD >22 mm/m^2	Propensity scores included the following 10 covariates: age, sex, hypertension,	Post-operative: Cardiovascular mortality or heart failure	Potential prognostic factor indirectness: threshold used is different to that specified in protocol

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
	N=356 (number asymptomatic unclear) Consecutive patients operated on between January 1995 and December 2014 at single centre		LVESD/BSA ≤22 mm/m^2 (referent)	chronic obstructive pulmonary disease, glomerular filtration rate >60 ml/min/1.73 m2, bicuspid aortic valve, type I and type II aortic regurgitation, history of stroke and history of atrial fibrillation. These IPWs were then used within the Cox multivariate model to obtain unbiased estimates of hazards.	Median (range) follow-up was 8 (0.1 to 21.8) years	
Maeda 2019[156]	Asymptomatic severe AR N=162 Consecutive patients undergoing isolated aortic valve replacement for severe chronic pure aortic regurgitation across 5 different but associated institutions between January 1991 and December 2010.	Multivariable Cox proportional hazards model	ESDI ≤25 mm/m^2 AND EDD ≤65 mm (referent) – early stage C ESDI >25 mm/m^2 OR EDD >65 mm – late stage C in paper	Age, gender, diabetes mellitus, chronic kidney disease and late stage C (based on classification of left ventricular dimensions, as described in the prognostic factor groups).	Post-operative: All-cause mortality (late death) Mean (SD) follow-up was 9.9 (5.3) years (range, 0-23 years)	Outcome definition unclear Indirect prognostic factor threshold
Pizarro 2011[209]	Asymptomatic severe AR	Multivariable logistic	End-systolic diameter/body surface	Multivariate regression models	LV systolic dysfunction	Potential prognostic factor indirectness:

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
	N=294 Consecutive patients from single centre.	regression model	area (ESD/BSA) ≥24 mm/m^2 End-systolic diameter/body surface area (ESD/BSA) <24 mm/m^2 (referent) End-diastolic diameter (EDD) ≥35 mm/m^2 End-diastolic diameter (EDD) <35 mm/m^2 (referent) In subgroup with BNP <130 pg/ml at baseline: BNP increased to ≥130 pg/ml at 1 year follow-up versus BNP remained <130 pg/ml at 1 year follow-up (referent)	incorporated clinical and echocardiographic variables that were demonstrated to be associated with the end-point on univariate analysis: BNP (different analyses using it as a continuous and categorical variable), ESD/BSA, EDD/BSA, effective regurgitant orifice area, atrial volume indexed by BSA, age, pulmonary artery systolic pressures, left ventricular ejection fraction and left ventricular volumes.	symptoms or death Mean (SD) follow-up was 46 (10) months in the derivation cohort and 38 (9) months in the validation cohort.	threshold different to that specified in protocol AVR performed in 31% during follow-up
Mitral regurgitation						
Arias 2013[6]	Asymptomatic moderate or severe organic MR (73% severe) without LV systolic dysfunction N=144 Unclear population source and recruitment period	Multivariable logistic regression model	Left atrial volume index (LAVI) ≥55 ml/m^2, n=48 Left atrial volume index <55 ml/m^2 (referent) , n=96	EROA ≥0.55 cm^2 and deceleration time ≤160 msec	Development of symptoms and/or LV dysfunction during follow-up. Median follow-up 2.76 years	Included a proportion with moderate MR LAVI threshold does not match protocol

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
Chenot 2009[51]	Asymptomatic severe MR undergoing mitral valve repair N=143 Consecutive patients from single institution between January 1990 and December 2001	Multivariable Cox proportional hazards model	LVEF <60% LVEF ≥60% (referent)	Age and diabetes mellitus potentially included in the multivariate model for cardiac mortality alongside LVEF <60%,	Post-operative: Cardiac mortality Median follow-up was 8 years	Unclear reporting of statistical analysis Included asymptomatic and mildly symptomatic
Coutinho 2014[59]	Asymptomatic or mildly symptomatic patients with severe degenerative mitral regurgitation and preserved left ventricular function submitted for surgery. Patients admitted between January 1992 and December 2012. N=382	Multivariable Cox proportional hazards model.	Presence of atrial fibrillation OR pulmonary hypertension, n=106 P2 prolapse present, n=268 Myxomatous valves, n=272	Mortality (late mortality): age, chronic obstructive pulmonary disease and presence of atrial fibrillation or pulmonary hypertension. Others are listed and may have been included but this is unclear as no multivariate results given for them in the table (myxomatous valves, tricuspid regurgitation ≥2+, left atrium dimension and P2 prolapse). Mitral reoperation: myxomatous valves, presence of atrial fibrillation or pulmonary	Post-operative: Mortality (late mortality) Cumulative follow-up for the entire cohort was 3732 patient-years (mean, 8.6 ± 7.5 years; range, 0.6-21.9 years); mean 9.8 years per person	NYHA class I or II and no further details on how mildly symptomatic was defined – downgraded for indirectness Late mortality: likely to mean after hospital discharge or beyond 30 days

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
				hypertension, P2 prolapse and chordal shortening. Others are listed and may have been included but this is unclear as no multivariate results given for them in the table (diabetes, anterior leaflet prolapse, posterior leaflet prolapse and posterior leaflet resection).		
Krauss 2006[135]	Asymptomatic severe MR N=128 Consecutive patients from single institution, prospectively enrolled and followed up.	Multivariable Cox proportional hazards model	Presence of new flail leaflet (NFL), n=30 Absence of new flail leaflet (NFL), n=98 Left ventricular end-systolic diameter (LVESD) >22 mm/m^2, n=23 Left ventricular end-systolic diameter (LVESD) ≤22 mm/m^2, n=105	New flail leaflet, left ventricular end-systolic diameter >22 mm/m^2, left ventricular end-diastolic diameter >35 mm/m^2, end-systolic diameter >45 mm, regurgitant volume >65 ml/beat, effective regurgitant orifice area >55 mm^2, atrial volume >120 cm3, E >120 cm/s and pulmonary arterial systolic pressure >35 mmHg. Factors that were significantly	Pre-operative: Occurrence of symptoms and/or left ventricular dysfunction Mean follow-up was 29 ± 12 months.	LVESD threshold does not match protocol

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
				associated with the end-point (P<0.10) on univariate analysis were included in the multivariate analysis		
Pizarro 2009[208]	Severe asymptomatic MR with LVEF >60% N=269 Consecutive patients from single institution, prospectively enrolled and followed up.	Multivariable logistic regression model And multivariable Cox proportional hazards model	Analysis 1 BNP ≥105 pg/ml BNP <105 pg/ml (referent) Analysis 2 BNP ≥105 pg/ml at 1 year in those with baseline <105 pg/ml BNP remaining <105 pg/ml at 1 year (referent) Analysis 3 LVESD >22 mm/m2, LVESD ≤22 mm/m2 (referent)	Unclear which variables included in each analysis. Factors considered: age >70 years, LVEF <68%, atrial fibrillation, new flail leaflet, end-diastolic diameter/BSA >35 mm/m2, end-systolic diameter/BSA >22 mm/m2, regurgitant volume >65 ml/beat, EROA >55 mm2, AV/BSA >70 cm3/m2, pulmonary artery systolic pressure >35 mm Hg	Development of congestive heart failure, or LV dysfunction or death during follow-up Mean follow-up 36 (8) and 31 (9) months in the of the derivation and validation sets, respectively.	Indirect outcome: composite measure 28% had surgery during follow-up
Yang 2015[276]	Severe asymptomatic primary MR N=104 Consecutive patients from single institution, prospectively enrolled and followed up.	Multivariable Cox proportional hazards model	Presence of atrial fibrillation (AF), n=20 Absence of atrial fibrillation (AF), n=84	Peak positive strain of the left atrium (LASp, continuous), age (continuous), left atrial volume index (LAVi, continuous), left ventricular end-systolic volume index (LVESVi, continuous) and AF	Cardiovascular mortality or mitral valve surgery (repair or replacement) caused by new-onset heart failure Heart failure Mean follow-up was 13.2 ± 9.5	Indirect outcome Excluded those with surgery planned. 19% had surgery during follow-up

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
					(IQR: 5.0-19.0) months.	

See Appendix D:for full evidence tables.

1.4.3 Quality assessment of clinical studies included in the evidence review

1.4.4.1 Aortic stenosis

Table 3: Clinical evidence summary: peak aortic jet velocity (Vmax)

Risk factor and outcome (population)	Number of studies (participants)	Relative effect (95% CI)	Quality of the evidence (GRADE)
≥5.0 m/s versus <5.0 m/s for predicting all-cause mortality Study 1 Median (IQR) follow-up: 38.0 (6–190) months. Study 2 Mean (SD; range) follow-up time: 27 (24; 2-224) (Minimally symptomatic or asymptomatic severe AS, plus preserved LVEF in study with 85% weight in analysis)	2 (n=1419)	HR 1.99 (1.51 to 2.62)	⨁⨁⨁⊖ MODERATE1 due to risk of bias
Vmax ≥5.5 m/s versus 4-4.49 m/s for predicting all-cause mortality Median (IQR) follow-up: 38.0 (6–190) months (Minimally symptomatic or asymptomatic severe AS, plus preserved LVEF).	1 (n=294)	HR 1.2 (1.01 to 1.43)	⨁⨁⊖⊖ LOW1,2 due to risk of bias, indirectness

Risk factor and outcome (population)	Number of studies (participants)	Relative effect (95% CI)	Quality of the evidence (GRADE)
Vmax ≥5.0 m/s versus 4-4.49 m/s for predicting all-cause mortality Median follow-up : 1336 (IQR, 966-1817) days (Severe asymptomatic AS not referred for AVR)	1 (n=456)	HR 1.23 (0.83 to 1.82)	⊕⊖⊖⊖ VERY LOW2,3,4
Vmax 5.0-5.49 m/s versus 4-4.49 m/s for predicting all-cause mortality Median (IQR) follow-up: 38.0 (6–190) months. (Minimally symptomatic or asymptomatic severe AS, plus preserved LVEF).	1 (n=333)	HR 1.36 (1.13 to 1.64)	⊕⊕⊖⊖ LOW1,2 due to risk of bias, indirectness
Vmax 4.5-4.99 m/s versus 4-4.49 m/s for predicting all-cause mortality Study 1 Median (IQR) follow-up: 38.0 (6–190) months. Study 2 Median follow-up : 1336 (IQR, 966-1817) days (Minimally symptomatic or asymptomatic severe AS)	2 (n=893)	HR 1.05 (0.63 to 1.74)	⊕⊖⊖⊖ VERY LOW3,4,5
≥5.0 m/s versus <5.0 m/s for predicting cardiac or CV mortality Median (IQR) follow-up: 1769 (1020–2423) days (Asymptomatic very severe AS - early surgery or conservative treatment)	1 (n=95)	HR 1.59 (1.22 to 2.07)	⊕⊕⊖⊖ LOW6,7 due to risk of bias
≥5.0 m/s versus <5.0 m/s for predicting cardiac or CV mortality Mean (SD; range) follow-up time was 27 (24; 2-224) (Asymptomatic severe AS)	1 (n=861)	HR 6.31 (2.51 to 15.86)	⊕⊕⊖⊖ LOW7,8 due to risk of bias

Risk factor and outcome (population)	Number of studies (participants)	Relative effect (95% CI)	Quality of the evidence (GRADE)
Vmax ≥5.0 m/s versus 4-4.49 m/s for predicting cardiac or CV mortality Median follow-up in whole sample: 1336 (IQR, 966-1817) days (Severe asymptomatic AS not referred for AVR)	1 (n=456)	HR 1.43 (0.88 to 2.32)	⨁⊖⊖⊖ VERY LOW2,3,4 due to risk of bias, indirectness, imprecision
Vmax 4.5-4.9 m/s versus 4-4.49 m/s for predicting cardiac or CV mortality Median follow-up in whole sample: 1336 (IQR, 966-1817) days. (Severe asymptomatic AS not referred for AVR)	1 (n=504)	HR 1.27 (0.79 to 2.04)	⨁⊖⊖⊖ VERY LOW3,4 due to risk of bias, imprecision
Vmax ≥5.0 m/s versus <5.0 m/s for predicting post-AVR mortality Mean (SD; range) follow-up time was 27 (24; 2-224) (Asymptomatic severe AS)	1 (n=834)	HR 2.2 (1.16 to 4.17)	⨁⨁⊖⊖ LOW8 due to risk of bias
Vmax ≥5.0 m/s versus 4-4.49 m/s for predicting aortic valve-related mortality Median follow-up in whole sample: 1336 (IQR, 966-1817) days. (Severe asymptomatic AS not referred for AVR)	1 (n=456)	HR 1.69 (0.94 to 3.04)	⨁⊖⊖⊖ VERY LOW2,3,4 due to risk of bias, indirectness, imprecision
Vmax 4.5-4.9 m/s versus 4-4.49 m/s for predicting aortic valve-related mortality Median follow-up in whole sample: 1336 (IQR, 966-1817) days. (Severe asymptomatic AS not referred for AVR)	1 (n=504)	HR 1.46 (0.81 to 2.63)	⨁⊖⊖⊖ VERY LOW3,5 due to risk of bias, imprecision

Risk factor and outcome (population)	Number of studies (participants)	Relative effect (95% CI)	Quality of the evidence (GRADE)
Vmax ≥5.0 m/s versus 4-4.49 m/s for predicting heart failure hospitalisation Median follow-up in whole sample: 1336 (IQR, 966-1817) days. (Severe asymptomatic AS not referred for AVR)	1 (n=456)	HR 1.65 (0.97 to 2.81)	⨁⊖⊖⊖ VERY LOW2,3,4 due to risk of bias, indirectness, imprecision
Vmax 4.5-4.9 m/s versus 4-4.49 m/s for predicting heart failure hospitalisation Median follow-up in whole sample: 1336 (IQR, 966-1817) days. (Severe asymptomatic AS not referred for AVR)	1 (n=504)	HR 1.19 (0.73 to 1.94)	⨁⊖⊖⊖ VERY LOW3,4 due to risk of bias, imprecision
Vmax ≥4.5 m/s versus <4.5 m/s for predicting mortality or AVR Mean follow-up was 22±18 months (Asymptomatic severe AS)	1 (n=128)	RR 1.1 (0.7 to 1.73)	⨁⊖⊖⊖ VERY LOW3,4 due to risk of bias, imprecision
Vmax ≥5.5 m/s versus 5.0-5.5 m/s for predicting cardiac mortality or AVR indication Median (IQR) follow-up was 41 (26-63) months (Asymptomatic very severe AS)	1 (n=116)	HR 1.88 (1.19 to 2.97)	⨁⨁⨁⊖ MODERATE1 due to risk of bias
Vmax ≥5.0 m/s versus 4.0-4.9 m/s for predicting cardiac mortality or AVR indication Median potential follow-up was 19.4 (IQR, 9.8-36.4) months (Asymptomatic severe AS aged >70 years)	1 (n=103)	HR 1.93 (1.16 to 3.21)	⨁⨁⊖⊖ LOW9 due to risk of bias

Risk factor and outcome (population)	Number of studies (participants)	Relative effect (95% CI)	Quality of the evidence (GRADE)
Vmax >4.0 m/s versus ≤4.0 m/s for predicting cardiac mortality or AVR indication Mean (SD) follow-up was 36 (27) months (Asymptomatic severe AS)	1 (n=103)	HR 2.58 (1.15 to 5.79)	⨁⨁⊖⊖ LOW3 due to risk of bias
Vmax ≥5.0 m/s versus <5.0 m/s for predicting sudden death Median follow-up of surviving patients in the entire cohort was 1334 (IQR, 1019-1701) days. (Asymptomatic severe AS)	1 (n=1808)	HR 2.36 (1.09 to 5.11)	⨁⊖⊖⊖ VERY LOW3,10 due to risk of bias, indirectness

[1] Majority of the evidence as at high risk of outcome measurement bias
[2] Indirect threshold comparison
[3] High risk of outcome reporting bias and <10 events per covariable in the analysis
[4] 95% CI crosses the null line
[5] I^2 >75% and only two studies so subgroups could not be explored; random effects model used
[6] High risk of outcome measurement bias and insufficient detail of the statistical analysis
[7] Study differences too great to pool data
[8] High risk of bias from insufficient study participation and high risk of outcome reporting bias
[9] High risk of outcome reporting bias and unclear study participation
[10] Indirect outcome measure

Table 4: Clinical evidence summary: Aortic valve area (AVA)

Risk factor and outcome (population)	No of Participants (studies) Follow up	Relative effect (95% CI)	Quality of the evidence (GRADE)
AVA≤0.6 versus >0.6 cm² for predicting all-cause mortality Estimated median follow-up was 48 months (Severe asymptomatic AS treated initially with medical management strategy)	1 (n=229)	HR 3.39 (1.8 to 6.38)	⨁⨁⨀⨀ LOW1 due to risk of bias
AVA≤0.6 versus >0.8 cm² for predicting all-cause mortality Median (IQR) follow-up duration of the surviving patients was 1203 (773–1575) days (Asymptomatic severe AS with normal LVEF managed conservatively)	1 (n=844)	HR 2.61 (1.96 to 3.48)	⨁⨁⨀⨀ LOW2,3 due to risk of bias, indirectness
0.8≥AVA>0.6 versus >0.8 cm² for predicting all-cause mortality Median (IQR) follow-up duration of the surviving patients was 1203 (773–1575) days (Asymptomatic severe AS with normal LVEF managed conservatively)	1 (n=1110)	HR 1.49 (1.17 to 1.9)	⨁⨁⨁⨀ MODERATE2 due to risk of bias
AVA≤0.6 versus >0.8 cm² for predicting cardiovascular mortality Median (IQR) follow-up duration of the surviving patients was 1203 (773–1575) days (Asymptomatic severe AS with normal LVEF managed conservatively)	1 (n=844)	HR 3.36 (2.34 to 4.82)	⨁⨀⨀⨀ VERY LOW3,4 due to risk of bias, indirectness
0.8≥AVA>0.6 versus >0.8 cm² for predicting cardiovascular mortality			

Risk factor and outcome (population)	No of Participants (studies) Follow up	Relative effect (95% CI)	Quality of the evidence (GRADE)
Median (IQR) follow-up duration of the surviving patients was 1203 (773–1575) days (Asymptomatic severe AS with normal LVEF managed conservatively)	1 (n=1110)	HR 1.48 (1.07 to 2.05)	⨁⨁⨀⨀ LOW3 due to risk of bias
AVA≤0.6 versus >0.8 cm² for predicting aortic valve-related mortality Median (IQR) follow-up duration of the surviving patients was 1203 (773–1575) days (Asymptomatic severe AS with normal LVEF managed conservatively)	1 (n=844)	HR 4.53 (2.97 to 6.91)	⨁⨀⨀⨀ VERY LOW3,4 due to risk of bias, indirectness
0.8≥AVA>0.6 versus >0.8 cm² for predicting aortic valve-related mortality Median (IQR) follow-up duration of the surviving patients was 1203 (773–1575) days (Asymptomatic severe AS with normal LVEF managed conservatively)	1 (n=1110)	HR 2.01 (1.31 to 3.08)	⨁⨁⨀⨀ LOW3 due to risk of bias
AVA≤0.6 versus >0.8 cm² for predicting heart failure hospitalisation Median (IQR) follow-up duration of the surviving patients was 1203 (773–1575) days (Asymptomatic severe AS with normal LVEF managed conservatively)	1 (n=844)	HR 1.95 (1.31 to 2.9)	⨁⨀⨀⨀ VERY LOW3,4 due to risk of bias, indirectness
0.8≥AVA>0.6 versus >0.8 cm² for predicting heart failure hospitalisation	1 (n=1110) days	HR 1.33 (0.96 to 1.84)	⨁⨀⨀⨀ VERY LOW3,5

Risk factor and outcome (population)	No of Participants (studies) Follow up	Relative effect (95% CI)	Quality of the evidence (GRADE)
Median (IQR) follow-up duration of the surviving patients was 1203 (773–1575) days (Asymptomatic severe AS with normal LVEF managed conservatively)			due to risk of bias, imprecision
AVA <0.6 vs. ≥0.6 cm^2 for predicting cardiac mortality or AVR indication Median (IQR) follow-up was 41 (26-63) months (Asymptomatic very severe AS)	1 (n=116)	HR 1.25 (0.77 to 2.03)	⨁⨁⊖⊖ LOW2,5 due to risk of bias, imprecision
AVA <0.75 vs. ≥0.75 cm^2 for predicting cardiac mortality or AVR indication Mean (SD) follow-up was 36 (27) months (Asymptomatic severe AS)	1 (n=103)	HR 1.48 (0.79 to 2.77)	⨁⊖⊖⊖ VERY LOW4,5 due to risk of bias, imprecision
AVAI (AVA index) <0.6 vs. ≥0.6 cm^2 for predicting cardiac mortality or AVR indication Mean (SD) follow-up was 36 (27) months (Asymptomatic severe AS)	1 (n=103)	HR 2.62 (1.09 to 6.3)	⨁⨁⊖⊖ LOW6 due to risk of bias

[1] High risk of bias from study participation and outcome measurement and <10 events per covariable in the analysis
[2] High risk of bias from outcome measurement
[3] Indirect threshold comparison
[4] High risk of bias from outcome measurement and <10 events per covariable in the analysis
[5] 95% CI crosses the null line
[6] Inadequate controlling for confounders and high risk of outcome measurement bias

1

2 **Table 5: Clinical evidence summary: left ventricular ejection fraction (LVEF)**

Risk factor and outcome (population)	No of Participants (studies) Follow up	Relative effect (95% CI)	Quality of the evidence (GRADE)
LVEF ≤50 vs >50% for predicting all-cause mortality Follow up unclear: survival curves up to 5 years (Asymptomatic severe AS who had surgery recommended)	1 (n=104)	HR 1.09 (1.03 to 1.15)	⊕⊕⊖⊖ LOW1 due to risk of bias
LVEF <55 vs ≥55% for predicting all-cause mortality Median (IQR) follow-up: 38.0 (6–190) months. (Severe AS with no or minimal symptoms, some managed surgically others medically)	1 (n=1378)	HR 2.18 (1.6 to 2.97)	⊕⊕⊕⊖ MODERATE2 due to risk of bias
LVEF <60 versus ≥60% for predicting all-cause mortality Mean (SD; range) follow-up: 27 (24; 2-224) months (Asymptomatic severe AS)	1 (n=834)	HR 5.01 (2.93 to 8.57)	⊕⊕⊖⊖ LOW3 due to risk of bias
LVEF <60 versus ≥60% for predicting cardiovascular mortality Mean (SD; range) follow-up: 27 (24; 2-224) months (Asymptomatic severe AS)	1 (n=834)	HR 4.47 (2.06 to 9.7)	⊕⊕⊖⊖ LOW3 due to risk of bias

Risk factor and outcome (population)	No of Participants (studies) Follow up	Relative effect (95% CI)	Quality of the evidence (GRADE)
LVEF <60 versus ≥60% for predicting post-AVR mortality Mean (SD; range) follow-up: 27 (24; 2-224) months (Asymptomatic severe AS)	1 (n=834)	Reported as not significant only	⨁⨁⨀⨀ LOW[3] due to risk of bias
AS-related death or heart failure hospitalisation at 1 year - <60 versus ≥60% Follow up: 1 year (Asymptomatic severe AS under watchful waiting)	1 (n=846)	OR 3.94 (2 to 7.76)	⨁⨁⨀⨀ LOW[4] due to risk of bias
LVEF <60% vs ≥60% for predicting sudden death Median follow-up: 1334 (IQR, 1019-1701) days. Not specified for the asymptomatic subgroup. (Asymptomatic severe AS)	1 (n=1808)	HR 1.76 (1.08 to 2.87)	⨁⨀⨀⨀ VERY LOW[4,5] due to risk of bias, indirectness

[1] Unclear prognostic factor measurement, inadequate controlling for confounders and post-hoc selection of thresholds
[2] Unclear if study participation was adequate
[3] High risk of outcome reporting bias and inadequate study participation
[4] High risk of outcome reporting bias and <10 events per covariable in the analysis
[5] Indirect outcome definition

Table 6: Clinical evidence summary: Left ventricular global longitudinal strain (LV-GLS)

Risk factor and outcome (population)	No of Participants (studies) Follow up	Relative effect (95% CI)	Quality of the evidence (GRADE)
LV-GLS ≤14.7 vs >14.7 for predicting all-cause mortality Median (IQR) follow-up 1.8 (0.9 to 2.8) years (Asymptomatic moderate/severe AS (82% severe))	1 (n=1067)	HR 2.62 (1.66 to 4.13)	⨁⨁⨁⨀ MODERATE1 due to risk of bias
LV-GLS ≤14.7 vs >14.7 for predicting all-cause mortality in those with LVEF ≥60% Median (IQR) follow-up 1.8 (0.9 to 2.8) years (Asymptomatic moderate/severe AS (82% severe))	1 (n=734)	HR 2.69 (1.53 to 4.73)	⨁⨁⨁⨀ MODERATE1 due to risk of bias
LV-GLS ≤15 vs >15 for predicting all-cause mortality in those with LVEF ≥50% Median (IQR) follow-up 42 (37-46) months (Minimally symptomatic or asymptomatic severe AS and LVEF ≥50%)	1 (n=332)	HR **Model 1:** 2.07 (95% CI 1.23 to 3.49) **Model 2:** 2.63 (95% CI 1.53 to 4.50 **Model 3:** 1.99 (95% CI 1.17 to 3.38)	⨁⨁⨁⨀ MODERATE2 due to risk of bias

[1] Unclear if all relevant studies in IPD meta-analysis have been identified and biases in primary studies not assessed or accounted for

[2] Inadequate controlling for confounders

Table 7: Clinical evidence summary: B-type natriuretic peptide (BNP)

Risk factor and outcome (population)	No of Participants (studies) Follow up	Relative effect (95% CI)	Quality of the evidence (GRADE)
BNP ratio 1 to 2 versus BNP ratio ≤1 for predicting all-cause mortality Mean follow-up of 4.3 (2.4) years (Asymptomatic severe AS)	1 (n=565)	HR 3.02 (1.31 to 6.96)	⨁⨁⊖⊖ LOW1 due to risk of bias
BNP ratio 2 to 3 versus BNP ratio ≤1 for predicting all-cause mortality Mean follow-up of 4.3 (2.4) years (Asymptomatic severe AS)	1 (n=565)	HR 4.64 (1.99 to 10.82)	⨁⨁⊖⊖ LOW1 due to risk of bias
BNP ratio ≥3 versus BNP ratio ≤1 for predicting all-cause mortality Mean follow-up of 4.3 (2.4) years (Asymptomatic severe AS)	1 (n=565)	HR 3.93 (2.4 to 6.43)	⨁⨁⊖⊖ LOW1 due to risk of bias
BNP >20pg/ml/year versus ≤20pg/ml/year for predicting adverse cardiac events Mean follow-up of 24 (17) months (Asymptomatic aortic stenosis of at least moderate severity and preserved LVEF)	1 (n=69)	HR 2.73 (1.27 to 5.87)	⨁⊖⊖⊖ VERY LOW2,3 due to risk of bias, indirectness

Risk factor and outcome (population)	No of Participants (studies) Follow up	Relative effect (95% CI)	Quality of the evidence (GRADE)
BNP 100-199 vs <100 pg/ml for predicting aortic valve-related death or hospitalisation due to HF Median follow-up duration 1190 (IQR: 732-1540) days (Asymptomatic severe AS not referred for AVR)	1 (n=295)	HR 1.97 (0.97 to 4)	⨁⊖⊖⊖ VERY LOW[4,5] due to risk of bias, imprecision
BNP 200-299 vs <100 pg/ml for predicting aortic valve-related death or hospitalisation due to HF Median follow-up duration 1190 (IQR: 732-1540) days (Asymptomatic severe AS not referred for AVR)	1 (n=243)	HR 3.59 (1.55 to 8.31)	⨁⊖⊖⊖ VERY LOW[4,6] due to risk of bias, indirectness
BNP ratio ≥300 versus <100 pg/ml for predicting aortic valve-related death or hospitalisation due to HF Median follow-up duration 1190 (IQR: 732-1540) days (Asymptomatic severe AS not referred for AVR)	1 (n=251)	HR 7.38 (3.21 to 16.97)	⨁⊖⊖⊖ VERY LOW[4,6] due to risk of bias, indirectness

[1] Unclear population source and participation, and <10 event per covariable in the analysis
[2] Insufficient controlling for confounders and unclear method of analysis
[3] Population included some with moderate AS
[4] Inadequate study participation due to lack of BNP data, high risk of outcome reporting bias and inadequate controlling for confounders
[5] 95% CI crosses the null line
[6] Indirect threshold comparison

Table 8: Clinical evidence summary: Composite indicators

Risk factor and outcome (population)	No of Participants (studies) Follow up	Relative effect (95% CI)	Quality of the evidence (GRADE)
High gradient AS and EF<50% or very HG-AS and EF ≥50% vs HG-AS and EF ≥50% or LG-AS for predicting all-cause mortality Median follow-up: 1360 (IQR: 1069-16669) days (Asymptomatic severe AS with normal LVEF managed conservatively)	1 (n=1512)	HR 1.45 (1.08 to 1.95)	⊕⊕⊕⊖ MODERATE1 due to risk of bias
High gradient AS with preserved ejection fraction (HGpEF) vs low gradient (LG) AS for predicting all-cause mortality Median follow-up: 1360 (IQR: 1069-16669) days (Asymptomatic severe AS with normal LVEF managed conservatively)	1 (n=1390)	HR 1.42 (1.14 to 1.77)	⊕⊕⊕⊖ MODERATE1 due to risk of bias
LG AS with reduced ejection fraction (LGrEF) vs with preserved ejection fraction (LGpEF) for predicting all-cause mortality Median follow-up: 1360 (IQR: 1069-16669) days (Asymptomatic severe AS with normal LVEF managed conservatively)	1 (n=892)	HR 2.74 (1.99 to 3.77)	⊕⊕⊕⊖ MODERATE1 due to risk of bias
High gradient AS and EF<50% or very HG-AS and EF ≥50% vs HG-AS and EF ≥50% or LG-AS for predicting cardiovascular mortality Median follow-up: 1360 (IQR: 1069-16669) days (Asymptomatic severe AS with normal LVEF managed conservatively)	1 (n=1512)	HR 1.84 (1.28 to 2.65)	⊕⊕⊕⊖ MODERATE1 due to risk of bias
HGpEF vs LG-AS for predicting cardiovascular mortality			

Risk factor and outcome (population)	No of Participants (studies) Follow up	Relative effect (95% CI)	Quality of the evidence (GRADE)
Median follow-up: 1360 (IQR: 1069-16669) days (Asymptomatic severe AS with normal LVEF managed conservatively)	1 (n=1390)	HR 1.56 (1.18 to 2.06)	⨁⨁⨁⨀ MODERATE1 due to risk of bias
LGrEF vs LGpEF for predicting cardiovascular mortality Median follow-up: 1360 (IQR: 1069-16669) days (Asymptomatic severe AS with normal LVEF managed conservatively)	1 (n=892)	HR 3.23 (2.13 to 4.9)	⨁⨁⨀⨀ LOW2 due to risk of bias
High gradient AS and EF<50% or very HG-AS and EF ≥50% vs HG-AS and EF ≥50% or LG-AS for predicting aortic valve-related mortality - Median follow-up: 1360 (IQR: 1069-16669) days (Asymptomatic severe AS with normal LVEF managed conservatively)	1 (n=1512)	HR 2.34 (1.52 to 3.6)	⨁⨁⨁⨀ MODERATE1 due to risk of bias
HGpEF vs LG-AS for predicting aortic valve-related mortality Median follow-up: 1360 (IQR: 1069-16669) days (Asymptomatic severe AS with normal LVEF managed conservatively)	1 (n=1390)	HR 1.77 (1.23 to 2.55)	⨁⨁⨀⨀ LOW2 due to risk of bias
LGrEF vs LGpEF for predicting aortic valve-related mortality	1 (n=892)	HR 4.06 (2.31 to 7.14)	⨁⨁⨀⨀ LOW2

Risk factor and outcome (population)	No of Participants (studies) Follow up	Relative effect (95% CI)	Quality of the evidence (GRADE)
Median follow-up: 1360 (IQR: 1069-16669) days (Asymptomatic severe AS with normal LVEF managed conservatively)			due to risk of bias
High gradient AS and EF<50% or very HG-AS and EF ≥50% vs HG-AS and EF ≥50% or LG-AS for predicting heart failure hospitalisation Median follow-up: 1360 (IQR: 1069-16669) days (Asymptomatic severe AS with normal LVEF managed conservatively)	1 (n=1512)	HR 1.96 (1.34 to 2.87)	⨁⨁⨁⨀ MODERATE1 due to risk of bias
HGpEF vs LG-AS for predicting heart failure hospitalisation Median follow-up: 1360 (IQR: 1069-16669) days (Asymptomatic severe AS with normal LVEF managed conservatively)	1 (n=1390)	HR 1.28 (0.94 to 1.74)	⨁⨁⨀⨀ LOW1,3 due to risk of bias, imprecision
LGrEF vs LGpEF for predicting heart failure hospitalisation Median follow-up: 1360 (IQR: 1069-16669) days (Asymptomatic severe AS with normal LVEF managed conservatively)	1 (n=892)	HR 2.37 (1.46 to 3.85)	⨁⨁⨀⨀ LOW2 due to risk of bias

[1] High risk of outcome reporting bias
[2] High risk of outcome reporting bias and <10 events per covariable in the analysis
[3] 95% CI crosses the null line

1.4.4.2 Aortic regurgitation

Table 9: Clinical evidence summary: Left ventricular ejection fraction (LVEF)

Risk factor and outcome (population)	No of Participants (studies) Follow up	Relative effect (95% CI)	Quality of the evidence (GRADE)
LVEF <55 versus ≥55% for predicting cardiovascular mortality or heart failure Median (range) follow-up was 8 (0.1 to 21.8) years (Asymptomatic severe AR)	1 (n unclear)	HR 4.13 (1.65 to 10.34)	⨁⨁⊖⊖ LOW[1] due to risk of bias

[1] High risk of outcome measurement bias and lack of detail on baseline characteristics of asymptomatic group

Table 10: Clinical evidence summary: Left ventricular dimensions

Risk factor and outcome (population)	No of Participants (studies) Follow up	Relative effect (95% CI)	Quality of the evidence (GRADE)
Indexed end systolic diameter (ESDI) >25 mm/m^2 OR end diastolic diameter (EDD) >65 mm vs. ESDI ≤25 mm/m^2 AND EDD ≤65 mm for predicting all-cause mortality (late death) Mean (SD) follow-up was 9.9 (5.3) years (range, 0-23 years) (Asymptomatic severe AR)	1 (n=162)	HR 1.99 (0.92 to 4.3)	⨁⊖⊖⊖ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision
Left ventricular end systolic diameter (LVESD) >22 mm/m^2 vs. LVESD/body surface area (BSA) ≤22 mm/m^2 for predicting cardiovascular mortality or heart failure	1 (n unclear)	HR 2.46 (1.07 to 5.66)	⨁⨁⊖⊖ LOW[1]

Risk factor and outcome (population)	No of Participants (studies) Follow up	Relative effect (95% CI)	Quality of the evidence (GRADE)
Median (range) follow-up was 8 (0.1 to 21.8) years (Asymptomatic severe AR)			due to risk of bias
ESD/BSA ≥24 mm/m2 vs. ESD/BSA <24 mm/m^2 for predicting LV systolic dysfunction symptoms or death Mean (SD) follow-up was 46 (10) months in the derivation cohort and 38 (9) months in the validation cohort. (Asymptomatic severe AR)	2 (n=294)	OR 3.4 (2.17 to 5.33)	⨁⨁⊖⊖ LOW[4] due to risk of bias
End diastolic diameter (EDD) ≥35 vs. <35 mm/m^2 for predicting LV systolic dysfunction symptoms or death Mean (SD) follow-up was 46 (10) months (Asymptomatic severe AR)	1 (n=160)	OR 2.1 (0.88 to 5.01)	⨁⊖⊖⊖ VERY LOW[3,4] due to risk of bias, imprecision

[1] High risk of outcome reporting bias and <10 events per covariable in the analysis
[2] Indirect prognostic factor definition
[3] 95% CI crosses null line
[4] Inadequate description of outcome measurement and recruitment, and inadequate controlling for confounders

Table 11: Clinical evidence summary: B-type natriuretic peptide (BNP)

Risk factor and outcome (population)	No of Participants (studies) Follow up	Relative effect (95% CI)	Quality of the evidence (GRADE)

Risk factor and outcome (population)	No of Participants (studies) Follow up	Relative effect (95% CI)	Quality of the evidence (GRADE)
BNP increase to ≥130 pg/ml vs retained <130 pg/ml at 1 year for predicting LV systolic dysfunction symptoms or death Mean (SD) follow-up was 46 (10) months in the derivation cohort and 38 (9) months in the validation cohort. (Asymptomatic severe AR)	2 (n=218)	HR 7.89 (4.81 to 12.94)	⨁⨁⊖⊖ LOW due to risk of bias1

[1]Inadequate description of outcome measurement and recruitment, and inadequate controlling for confounders

1.4.4.3 Mitral regurgitation

Table 12: Clinical evidence summary: Left ventricular ejection fraction (LVEF)

Outcomes	No of Participants (studies) Follow up	Relative effect (95% CI)	Quality of the evidence (GRADE)
LVEF <60 versus ≥60% for predicting cardiac mortality - Median follow-up: 8 years (Asymptomatic severe MR undergoing mitral valve repair)	1 (n=143)	HR 3.9 (1.1 to 13.83)	⨁⨁⊖⊖ LOW1 due to risk of bias

[1] High risk of outcome measurement bias and inadequate controlling for confounders, and < 10 events per covariable in analysis

Table 13: Clinical evidence summary: Left ventricular end systolic diameter (LVESD)

Risk factor and outcome (population)	No of Participants (studies) Follow up	Relative effect (95% CI)	Quality of the evidence (GRADE)
LVESD >22 vs ≤22 mm/m² for predicting onset of symptoms and/or LV dysfunction Mean follow-up: 29 ± 12 months (Asymptomatic severe MR)	1 (n=128)	HR 4.5 (1.8 to 11.25)	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, indirectness
LVESD >22 vs ≤22 mm/m² for predicting onset of symptoms and/or LV dysfunction Mean follow-up 36 (8) and 31 (9) months in the of the derivation and validation sets (Severe asymptomatic MR with LVEF >60%)	1 (n=296 (1 study; derivation and validation cohorts)	OR 3.2 (2.06 to 4.97)[4]	⊕⊖⊖⊖ VERY LOW2,3 due to risk of bias, indirectness

[1] High risk of outcome measurement bias and inadequate controlling for confounders, and < 10 events per covariable in analysis
[2] Indirect prognostic factor and population definitions
[3] High risk of bias from limitations with study participation and high risk of bias from lack of clarity on confounders adjusted for and likely to be <10 events per covariable in the analysis.
[4] Upper limit of 95% CIs calculated in RevMan do not match those reported in the study, as these were asymmetrical around the point estimate.

Table 14: Clinical evidence summary: Left atrial volume index (LAVI)

Risk factor and outcome (population)	No of Participants (studies) Follow up	Relative effect (95% CI)	Quality of the evidence (GRADE)
LAVI ≥55ml/m² vs LAVI <55ml/m² for predicting onset of symptoms and/or LV dysfunction	1 (n=144)	OR 2.26 (1.04 to 4.88)	⊕⊖⊖⊖ VERY LOW1,2

Risk factor and outcome (population)	No of Participants (studies) Follow up	Relative effect (95% CI)	Quality of the evidence (GRADE)
Median follow-up 2.76 years (Asymptomatic moderate or severe organic MR (73% severe) without LV systolic dysfunction)			due to risk of bias, indirectness

[1] High risk of bias because source population and recruitment are unclear and high risk of bias from inadequate controlling for confounders
[2] Indirect prognostic factor definition

Table 15: Clinical evidence summary: Flail leaflet

Risk factor and outcome (population)	No of Participants (studies) Follow up	Relative effect (95% CI)	Quality of the evidence (GRADE)
Presence vs absence of new FL for predicting onset of symptoms and/or LV dysfunction Mean follow-up: 29 ± 12 months (Asymptomatic severe MR)	1 (n=128).	HR 1.6 (0.3 to 8.53)	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision

[1] High risk of outcome measurement bias and inadequate controlling for confounders, and < 10 events per covariable in analysis
[2] 95% CI crosses null line

Table 16: Clinical evidence summary: Posterior prolapse

Risk factor and outcome (population)	No of Participants (studies) Follow up	Relative effect (95% CI)	Quality of the evidence (GRADE)
Presence versus absence of P2 prolapse for predicting mitral re-operation Mean follow-up 9.8 years (Asymptomatic or mildly symptomatic severe MR and preserved left ventricular function submitted for surgery)	1 (n=382)	HR 0.06 (0.01 to 0.36)	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, indirectness

[1] High risk of outcome measurement bias and inadequate controlling for confounders, and < 10 events per covariable in analysis
[2] Indirect population (NYHA I and II) and outcome measure

Table 17: Clinical evidence summary: Ruptured chordae

Risk factor and outcome (population)	No of Participants (studies) Follow up	Relative effect (95% CI)	Quality of the evidence (GRADE)
Presence versus absence of myxomatous valves for predicting mitral re-operation Mean follow-up 9.8 years (Asymptomatic or mildly symptomatic severe MR and preserved left ventricular function submitted for surgery)	1 (n=382)	HR 0.07 (0.01 to 0.49)	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, indirectness

[1] High risk of outcome measurement bias and inadequate controlling for confounders, and < 10 events per covariable in analysis
[2] Indirect population (NYHA I and II), prognostic factor and outcome definition

Table 18: Clinical evidence summary: Atrial fibrillation

Risk factor and outcome (population)	No of Participants (studies) Follow up	Relative effect (95% CI)	Quality of the evidence (GRADE)
Presence of atrial fibrillation OR pulmonary hypertension, versus absence of atrial fibrillation AND pulmonary hypertension for predicting mortality Mean follow-up 9.8 years (Asymptomatic or mildly symptomatic severe MR and preserved left ventricular function submitted for surgery)	1 (n=382)	HR 2.54 (1.17 to 5.51)	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, indirectness
Presence vs absence of AF for predicting cardiovascular mortality or mitral valve surgery (repair or replacement) caused by new-onset heart failure Mean follow-up was 13.2 ± 9.5 (IQR: 5.0-19.0) months. (Severe asymptomatic primary MR)	1 (n=104)	HR 1.16 (0.33 to 4.08)	⊕⊖⊖⊖ VERY LOW1,3 due to risk of bias, imprecision
Presence vs absence of AF for predicting heart failure Mean follow-up was 13.2 ± 9.5 (IQR: 5.0-19.0) months. (Severe asymptomatic primary MR)	1 (n=104)	HR 1.19 (0.38 to 3.73)	⊕⊖⊖⊖ VERY LOW1,3 due to risk of bias, imprecision
Presence of atrial fibrillation OR pulmonary hypertension, versus absence of atrial fibrillation AND pulmonary hypertension for predicting mitral re-operation Mean follow-up 9.8 years (Asymptomatic or mildly symptomatic severe MR and preserved left ventricular function submitted for surgery)	1 (n=382)	HR 4.2 (1.1 to 16.04)	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, indirectness

[1] High risk of outcome measurement bias and inadequate controlling for confounders, and < 10 events per covariable in analysis
[2] Indirect population (includes NYHA I and II) and indirect prognostic factor definition
[3] 95% CI crosses the null line

Table 19: Clinical evidence summary: BNP

Risk factor and outcome (population)	No of Participants (studies) Follow up	Relative effect (95% CI)	Quality of the evidence (GRADE)
BNP ≥105 pg/ml vs BNP <105 pg/ml for predicting onset of CHF, LV dysfunction or death Mean follow-up 36 (8) and 31 (9) months in the of the derivation and validation sets (Severe asymptomatic MR with LVEF >60%)	1 study; derivation and validation cohorts (n=296)	OR 4.28 (3.08 to 5.95)3	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, indirectness
Increase in BNP over 105 pg/ml at 1 year vs BNP remains <105 pg/ml at 1 year in subgroup with BNP <105 pg/ml at baseline for predicting onset of CHF, LV dysfunction or death Mean follow-up 36 (8) and 31 (9) months in the of the derivation and validation sets (Severe asymptomatic MR with LVEF >60%)	1 study; derivation and validation cohorts n=205	HR 9.6 (5.6 to 16.46)3	⊕⊕⊖⊖ LOW1 due to risk of bias

[1] High risk of bias from limitations with study participation and high risk of bias from lack of clarity on confounders adjusted for and likely to be <10 events per covariable in the analysis.
[2] Indirect prognostic factor definition
[3] Upper limit of 95% CIs calculated in RevMan do not match those reported in the study, as these were asymmetrical around the point estimate.

See Appendix F: for full GRADE tables.

1.5 Economic evidence

1.5.1 Included studies

No health economic studies were included.

1.5.2 Excluded studies

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

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

1.5.3 Health economic modelling

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

1.5.4 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[194]
Complex Echocardiogram	£375 (b)	NHS reference costs 2018/19[194]

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

1.6 The committee's discussion of the evidence

1.6.1 Interpreting the evidence

1.6.1.1 The outcomes that matter most

Indication for intervention was assessed based on prognosis for the following outcomes:

- Mortality
- Hospital admission for heart failure
- Reduced cardiac function

1.6.1.2 The quality of the evidence

No studies meeting the review protocol criteria were identified for mitral stenosis or tricuspid regurgitation. These populations were included in a research recommendation (see Appendix J.2 for details).

The quality of the evidence ranged from moderate to very low, with the majority of the evidence being of low or very low quality. Evidence was mainly downgraded due to risk of bias. Common limitations included the analysis being retrospective, based on registry data, so that the measurement of the indicators and outcomes were not the same for all study participants, a lack of accounting for confounders and no assessment of inter-rater reliability. The retrospective nature of the data often left it unclear whether all potentially eligible individuals were included or how many didn't have relevant data points recorded. Also, much of the evidence was from multivariable analysis with too few events per covariate for the estimates to be reliable.

Some studies were also from indirect populations, including some with mild symptoms. The committee agreed that in the studies that defined these as symptoms not related to the heart valve disease, no downgrading of the evidence was necessary, but if it was unclear how minimal symptoms were defined or if they were related to the valve disease, the evidence was downgraded for population indirectness. It is noteworthy that the evidence is an indirect way of assessing at what point interventions are indicated. It informs the prognosis for poor

outcomes with or without intervention among people that have reached a certain level of abnormality for measured parameters (for example, an LVEF <50% or <60% on echocardiography) compared with those that have not reached the same level of abnormality for these parameters. However, not all studies limited to the prediction of outcomes either pre- or post-intervention and there is no comparison of intervention versus no intervention in particular prognostic groups. Therefore, it is not clear if intervention would improve outcome in groups with poor prognosis.

Based on these limitations in the included evidence, recommendations were limited to consider recommendations.

1.6.13 Benefits and harms

Aortic stenosis

The committee discussed that the hearts of people with aortic stenosis are coping with a significant pressure load, and the development of symptoms due to aortic stenosis indicates a dramatic worsening of prognosis (without intervention). Identifying signs of early cardiac decompensation (prior to symptom onset) that are associated with worse outcomes would be beneficial for identifying patients for potential intervention, while still asymptomatic. It is already established practice to consider intervention if reduced cardiac function is observed. Surgical intervention is specified, as transcatheter interventions are currently only indicated for symptomatic patients.

A peak aortic jet velocity of ≥5.0 m/s was shown to be a risk factor for all-cause and cardiovascular mortality, and sudden death in people with asymptomatic severe AS who have not had an aortic valve intervention. Other reported thresholds were less indicative of increased mortality risk without intervention and also did not predict heart failure hospitalisation. Evidence on the composite outcome of mortality or AVR was also discussed by the committee. A peak aortic jet velocity of ≥5.5 m/s, ≥5.0 m/s and >4.0 m/s were all found to be predictive of this outcome. The committee agreed that this supports the use of the ≥5.0 m/s threshold, and was insufficient to suggest the use of an alternative threshold.

One study also reported post-aortic valve replacement mortality to be higher among those with a baseline peak aortic jet velocity of ≥5.0 m/s. The committee agreed it is sensible to assume that if a factor is associated with poor outcome after surgery, this suggests that intervention should have been earlier. Therefore, the committee interpreted this as supporting the use of this threshold as an indicator for intervention to prevent any further valve deterioration and worsening of prognosis, which would be the biologically plausible disease pathway.

Aortic valve area ≤0.6 versus >0.6 cm^2 was also a risk factor for all-cause mortality, before or after aortic valve intervention. Additionally, the threshold of ≤0.6 versus >0.8cm^2 showed a greater risk for cardiovascular or aortic valve-related mortality and heart failure hospitalization than the comparison of >0.6-0.8 versus >0.8cm^2. This is consistent with the data for a peak aortic jet velocity of >5.0m/sec, as these two measures / thresholds are both indicators of very severe aortic stenosis and often co-exist.

A left ventricular ejection fraction (LVEF) <60% was shown to be the strongest indicator of all-cause mortality, with the relative risk being greater in this group than for <55 versus ≥55% or ≤50 vs >50%. This was supported by evidence of increased risk of cardiovascular mortality, sudden death, and AS-related death or heart failure hospitalisation among those with LVEF <60% versus ≥60%. The committee noted that the threshold of 50% showed to be a weak predictor of mortality, with a very small effect size, which could be because the difference in outcome is diluted by the referent group (>50%) containing a high proportion with poor outcome as many people with severe AS have a LVEF in the 50-60% range, making this a poor cut-off for discriminating need for intervention. The committee noted that established practice is to consider intervention for ‘reduced’ cardiac function (generally

considered to be an EF of < 50, so a threshold of <60% would result in a change in practice for some patients.

One study also reported post-aortic valve replacement mortality not to be significantly different among those with a baseline LVEF <60 versus ≥60%.

One individual patient data (IPD) meta-analysis of 10 original studies derived a threshold of global longitudinal strain of ≤14.7% and found this to be a risk factor for all-cause mortality, even among the subgroup with preserved LVEF ≥60%. One further study found evidence for global longitudinal strain of ≤15% as a risk factor for all-cause mortality, after adjusting for aortic valve intervention. The committee discussed global longitudinal strain as a potentially useful indicator. However, there are concerns about the reproducibility of the measure in individual patients and across manufacturers of echocardiogram systems. Therefore, in the absence of validation of the threshold to be used, they agreed that further research is required before making a recommendation for practice. A research recommendation was made (see Appendix J.2 for details).

Elevation of BNP above the normal level in those with preserved LVEF (>50%) was a risk factor for all-cause mortality before or after intervention. It was unclear if the LVEF changed during follow-up, but LVEF was adjusted for as a covariate in the analysis. The largest increase in risk was seen for BNP 2-3-times the normal level. The risk associated with BNP was supported by indirect evidence from 2 additional studies. One study reported the less critical outcome of adverse cardiac events in a very small cohort, using the threshold of >20pg/ml increase in BNP level per year. Although the committee were interested in the change in BNP over time, this evidence was limited by the small sample size, indirect population including moderate as well as severe aortic stenosis and indirect composite outcome, and so it was agreed that this study was insufficient to inform the threshold to indicate intervention. The other used the composite outcome of AS-related death or heart failure hospitalization and compared centiles with the risk among those with <100pg/ml BNP. This supported the link between increasing BNP level and increasing risk of poor outcome but was not suitable evidence for determining the optimal threshold because of the comparisons used, including a low threshold for the referent group that would have poor specificity. Based on this evidence and the experience of the committee that BNP is a useful early marker of myocardial decompensation, the committee agreed to recommend BNP at least 2-times the upper limit of normal as an indicator for intervention. BNP is not currently used as an indication for intervention in asymptomatic patients, so this would reflect a change in practice for some patients.

Based on the above evidence the committee made recommendations for referral for surgical intervention to be considered in adults with severe asymptomatic aortic stenosis and any of the following: peak aortic jet velocity >5.0 m/s, AVA <0.6 cm^2, LVEF <60% or BNP /NT-proBNP level >2-times the upper limit of normal. Surgical intervention was specified because this is the only option for aortic valve replacement in people without symptoms. TAVI research is limited to symptomatic patients only. Therefore, all evidence for “early” aortic valve replacement before symptoms occur is in patients suitable for surgery. This decision is only applicable to patients young enough and without significant comorbidities who have a good enough baseline prognosis to be significantly affected by the improved prognosis afforded by earlier intervention as indicated by the factors recommended. Recommendations were limited to consider recommendations based on the limitations of the included evidence, including most evidence being low-very low quality, as described in the ‘quality of the evidence’ section above.

Aortic regurgitation

The committee discussed that the hearts of people with aortic regurgitation are coping with a significant volume load and it is established practice to consider intervention if reduced

cardiac function is observed (given that cardiac function should be at the higher end of the normal range). It was also noted that people with aortic regurgitation suffer more than other types of heart valve disease if intervention is delayed and are generally a younger cohort, so have more to gain from timely intervention. Surgical intervention is specified as i) there is no current accepted transcatheter intervention for aortic regurgitation, and ii) transcatheter interventions are currently only indicated for symptomatic patients.

Regarding LVEF, the only threshold assessed in the evidence was <55% versus ≥55%, which was a risk factor for the composite outcome of post-intervention cardiovascular mortality or heart failure. Therefore, the committee agreed that the threshold for considering referral should be LVEF<55% due to the magnitude of the increased risk of poor outcome in this group. They agreed that, although the classically recommended threshold is <50%, the <55% threshold is already widely used in practice, and that a recommendation at this threshold would not have a large impact on current practice. The committee discussed the lack of evidence for other possible thresholds but agreed that a research recommendation in this area would not serve the interests of people with aortic regurgitation given the available evidence from one study and their clinical experience of the threshold of LVEF<55% being used in practice.

Regarding left ventricular dimensions, indexed end systolic diameter (ESDI) was agreed to be another measure of systolic function, not just of dilatation, and may be useful in addition to other measures. The committee considered the evidence that showed an increased risk of post-intervention cardiovascular mortality or heart failure with ESDI >22 mm/m^2 and an increased risk of left ventricular systolic dysfunction or death with ESDI >24 mm/m^2. They agreed that the threshold of >24 mm/m^2 should be recommended as an indicator for intervention. This was because on the basis of limited evidence this is the more conservative threshold to use, and the group with ESDI >24 mm/m^2 are, in the committees' opinion, likely to include most of those who would derive benefit from intervention, with few cases likely to be missed between 22 and 24 mm/m^2. Further, given the asymptomatic nature of the patient group and the morbidity and mortality from cardiac surgery, a slightly conservative approach was felt to be appropriate.

Regarding BNP, despite one study demonstrating a large increased risk in those with BNP levels above 130 pg/ml at 1 year, the committee noted that this was from 1 small study, with very few people having this increase in BNP (7 in total in the study). Also, the threshold chosen was agreed to represent any increase above normal. Given this limited evidence the committee agreed that this is another area for future research and made a research recommendation (see Appendix J.1 for details).

Recommendations were limited to consider recommendations based on the limitations of the included evidence, including most evidence being low-very low quality, as described in the 'quality of the evidence' section above.

Mitral regurgitation

There was evidence that LVEF <60% was a risk factor for increased post-repair cardiac mortality. Although this was based on a single study, this threshold reflects current practice and the committee was aware of evidence from longitudinal studies that if the LVEF drops below 60% it is important to intervene. Therefore, the committee agreed that LVEF <60% should be an indicator for intervention to avoid further deterioration before intervention that could limit the benefit of intervention.

There was also evidence from 2 studies that LVESDI >22 mm/m^2 was a risk factor for poor outcome (onset of symptoms and/or left ventricular dysfunction in one study and onset of congestive heart failure, left ventricular dysfunction or death in another study) without valve intervention, and so this was agreed to be a good indicator for intervention. The committee noted that measurement of LVESD is common in current practice and is easier to measure than LVEF, thus adding certainty to the LVEF measurement. Although the indexed

measurement is not commonly used the committee agreed that this change is appropriate to account for differences in BMI based on the available evidence.

The committee discussed the evidence about valve morphology (flail leaflet, and ruptured chordae), BNP and left atrial volume index but agreed that it was neither robust nor direct enough to dictate indictors for intervention. Specifically, the committee noted the lack of post-operative outcome data, making it unclear whether people with a high LAVI or BNP score do worse after surgery. Regarding BNP, despite one study demonstrating a large increased risk in those with BNP levels above 105 pg/ml, the committee noted that this was from 1 small study. Also, the threshold chosen was agreed to represent any increase above normal. Given this limited evidence the committee agreed that this is another area for future research (see Appendix J.1 for details).

Similarly, the conflicting findings between studies and outcomes for atrial fibrillation, and the inability to separate the effect of atrial fibrillation and pulmonary hypertension in one study meant it was not possible to recommend these as indicators. However, the evidence did suggest that the presence of pulmonary hypertension (systolic pulmonary artery pressure >50 mmHg) or atrial fibrillation increases the risk of post-repair mortality and that morphology suitable for repair, such as P2 prolapse, reduces the risk of re-operation Therefore, these were included in the recommendation as factors that would further support a decision to intervene in people who also have markers of early myocardial decompensation.

As for aortic stenosis, referring asymptomatic patients for intervention means referring them "early" on prognostic grounds. Patients need to be young enough and without significant comorbidities to have a good enough baseline prognosis to benefit from the improved prognosis afforded by earlier intervention. Therefore, surgical intervention is currently the only option considered.

Recommendations were limited to consider recommendations based on the limitations of the included evidence, including most evidence being low-very low quality, as described in the 'quality of the evidence' section above.

1.6.22 Cost effectiveness and resource use

There was no evidence of clinical effectiveness or cost effectiveness for intervention at different thresholds. The committee made consensus recommendations to refer people at different thresholds, which predicted a significant worsening of outcomes, including survival.

The committee judged that these recommendations largely reflect current best practice, though there is local variation and not all clinicians would currently be aware that all of these specific thresholds should lead to referral for intervention.

However, the threshold of LVEF <60% for aortic stenosis intervention does represent a significant change from current practice, which is <50% in some centres. However, when LVEF starts to decline, it does so quite quickly, moving from 60% to 50% in under a year in the experience of the committee. Therefore, this will mean earlier rather than additional intervention, with subsequent improvement in survival and quality of life. In addition, the inclusion of BNP as an indicator for potential early intervention is new. Again, for most patients this will mean earlier intervention rather than additional intervention. Although there are some risks with intervention as well as health care cost, it is expected that there will be a significant improvement in survival and quality of life for patients. It is also possible that the cost of earlier intervention could be partially offset by reduced admissions, although there would also be increased costs in the added years of life. The cost effectiveness of this earlier intervention is difficult to quantify.

1.6.8 Other factors the committee took into account

The committee were aware of evidence comparing early surgery in the absence of any indications with watchful waiting until symptoms were identified, particularly in mitral regurgitation. These studies did not match the protocol for the current review and so were not included as they do not inform the choice of indicators for intervention among the asymptomatic severe cohort. However, the committee noted that these studies support early intervention in the absence of symptoms or any other indicators.

1.7 Recommendations supported by this evidence review

This evidence review supports recommendations 1.3.2, 1.3.7 and 1.3.8 and the research recommendations on techniques to determine the need for intervention.

References

1. Abdel Fattah EM, Girgis HY, El Khashab K, Ashour ZA, Ezzat GM. B-type natriuretic peptide as an index of symptoms and severity of chronic rheumatic mitral regurgitation. Heart Views. 2016; 17(1):7-12

2. Alashi A, Khullar T, Mentias A, Gillinov AM, Roselli EE, Svensson LG et al. Long-term outcomes after aortic valve surgery in patients with asymptomatic chronic aortic regurgitation and preserved LVEF: impact of baseline and follow-up global longitudinal strain JACC: Cardiovascular Imaging. 2020; 13(1 Pt 1):12-21

3. Alashi A, Mentias A, Abdallah A, Feng K, Gillinov AM, Rodriguez LL et al. Incremental prognostic utility of left ventricular global longitudinal strain in asymptomatic patients with significant chronic aortic regurgitation and preserved left ventricular ejection fraction. JACC: Cardiovascular Imaging. 2018; 11(5):673-682

4. Alashi A, Mentias A, Patel K, Gillinov AM, Sabik JF, Popovic ZB et al. Synergistic utility of brain natriuretic peptide and left ventricular global longitudinal strain in asymptomatic patients with significant primary mitral regurgitation and preserved systolic function undergoing mitral valve surgery. Circulation Cardiovascular Imaging. 2016; 9(7)

5. Antonini-Canterin F, Di Nora C, Cervesato E, Zito C, Carerj S, Ravasel A et al. Value of ejection fraction/velocity ratio in the prognostic stratification of patients with asymptomatic aortic valve stenosis. Echocardiography. 2018; 35(12):1909-1914

6. Arias A, Pizarro R, Oberti P, Falconi M, Lucas L, Sosa F et al. Prognostic value of left atrial volume in asymptomatic organic mitral regurgitation. Journal of the American Society of Echocardiography. 2013; 26(7):699-705

7. Avakian SD, Grinberg M, Ramires JA, Mansur AP. Outcome of adults with asymptomatic severe aortic stenosis. International Journal of Cardiology. 2008; 123(3):322-327

8. Avierinos JF, Gersh BJ, Melton LJ, 3rd, Bailey KR, Shub C, Nishimura RA et al. Natural history of asymptomatic mitral valve prolapse in the community. Circulation. 2002; 106(11):1355-1361

9. Badhwar V, Peterson ED, Jacobs JP, He X, Brennan JM, O'Brien SM et al. Longitudinal outcome of isolated mitral repair in older patients: results from 14,604 procedures performed from 1991 to 2007. Annals of Thoracic Surgery. 2012; 94(6):1870-1877; discussion 1877-1879

10. Badran AA, Vohra HA, Livesey SA. Unoperated severe aortic stenosis: decision making in an adult UK-based population. Annals of the Royal College of Surgeons of England. 2012; 94(6):416-421

11. Bahler RC, Hawi R, Rovner A, Finkelhor RS, Thomas CL, Dawson NV. Predicting outcomes in patients with asymptomatic moderate to severe aortic stenosis. American Journal of Cardiology. 2018; 122(5):851-858

12. Banovic M, Brkovic V, Vujisic-Tesic B, Nedeljkovic I, Trifunovic D, Ristic A et al. Valvulo-arterial impedance is the best mortality predictor in asymptomatic aortic stenosis patients. Journal of Heart Valve Disease. 2015; 24(2):156-163

13. Banovic M, Iung B, Bartunek J, Asanin M, Beleslin B, Biocina B et al. Rationale and design of the Aortic Valve replAcemenT versus conservative treatment in

Asymptomatic seveRe aortic stenosis (AVATAR trial): a randomized multicenter controlled event-driven trial. American Heart Journal. 2016; 174:147-153

14. Banovic M, Iung B, Brkovic V, Nikolic S, Mitrovic P, Van Camp G et al. Silent coronary artery disease in asymptomatic patients with severe aortic stenosis and normal exercise testing. Coronary Artery Disease. 2020; 31(2):166-173

15. Barbieri A, Benfari G, Giubertoni E, Manicardi M, Bursi F, Rossi A et al. Degree of left ventricular dilatation at end-diastole: Correlation and prognostic utility of quantitative volumes by 2D-echocardiography versus linear dimensions in patients with asymptomatic aortic regurgitation. Echocardiography. 2020; 37(9):1336-1344

16. Baumgartner H, Iung B, Otto CM. Timing of intervention in asymptomatic patients with valvular heart disease. European Heart Journal. 2020; 41(45):4349–4356

17. Bergler-Klein J, Klaar U, Heger M, Rosenhek R, Mundigler G, Gabriel H et al. Natriuretic peptides predict symptom-free survival and postoperative outcome in severe aortic stenosis. Circulation. 2004; 109(19):2302-2308

18. Bergstra A, Simsek C, van den Heuvel AFM. Mitral regurgitation: when to intervene? : A historical perspective. Netherlands Heart Journal. 2020; 28(5):266-271

19. Bhattacharyya S, Hayward C, Pepper J, Senior R. Risk stratification in asymptomatic severe aortic stenosis: a critical appraisal. European Heart Journal. 2012; 33(19):2377-2387

20. Bhudia SK, McCarthy PM, Kumpati GS, Helou J, Hoercher KJ, Rajeswaran J et al. Improved outcomes after aortic valve surgery for chronic aortic regurgitation with severe left ventricular dysfunction. Journal of the American College of Cardiology. 2007; 49(13):1465-1471

21. Biem HJ, Detsky AS, Armstrong PW. Management of asymptomatic chronic aortic regurgitation with left ventricular dysfunction: a decision analysis. Journal of General Internal Medicine. 1990; 5(5):394-401

22. Bijvoet GP, Teske AJ, Chamuleau SAJ, Hart EA, Jansen R, Schaap J. Global longitudinal strain to predict left ventricular dysfunction in asymptomatic patients with severe mitral valve regurgitation: literature review. Netherlands Heart Journal. 2020; 28(2):63-72

23. Biner S, Rafique AM, Goykhman P, Morrissey RP, Naghi J, Siegel RJ. Prognostic value of E/E' ratio in patients with unoperated severe aortic stenosis. JACC: Cardiovascular Imaging. 2010; 3(9):899-907

24. Bing R, Everett RJ, Tuck C, Semple S, Lewis S, Harkess R et al. Rationale and design of the randomized, controlled Early Valve Replacement Guided by Biomarkers of Left Ventricular Decompensation in Asymptomatic Patients with Severe Aortic Stenosis (EVOLVED) trial. American Heart Journal. 2019; 212:91-100

25. Bohbot Y, Chadha G, Delabre J, Landemaine T, Beyls C, Tribouilloy C. Characteristics and prognosis of patients with significant tricuspid regurgitation. Archives of Cardiovascular Diseases. 2019; 112(10):604-614

26. Bohbot Y, de Meester de Ravenstein C, Chadha G, Rusinaru D, Belkhir K, Trouillet C et al. Relationship between left ventricular ejection fraction and mortality in asymptomatic and minimally symptomatic patients with severe aortic stenosis. JACC: Cardiovascular Imaging. 2019; 12(1):38-48

27. Bohbot Y, Guignant P, Rusinaru D, Kubala M, Marechaux S, Tribouilloy C. Impact of right ventricular systolic dysfunction on outcome in aortic stenosis. Circulation Cardiovascular Imaging. 2020; 13(1):e009802

28. Bohbot Y, Kowalski C, Rusinaru D, Ringle A, Marechaux S, Tribouilloy C. Impact of mean transaortic pressure gradient on long-term outcome in patients with severe aortic stenosis and preserved left ventricular ejection fraction. Journal of the American Heart Association. 2017; 6(6):e005850

29. Bohbot Y, Pasquet A, Rusinaru D, Delabre J, Delpierre Q, Altes A et al. Asymptomatic severe aortic stenosis with preserved ejection fraction: Early surgery versus conservative management. Journal of the American College of Cardiology. 2018; 72(23 Pt A):2938-2939

30. Bohbot Y, Rusinaru D, Delpierre Q, Marechaux S, Tribouilloy C. Risk stratification of severe aortic stenosis with preserved left ventricular ejection fraction using peak aortic jet velocity: An outcome study. Circulation Cardiovascular Imaging. 2017; 10(10):10

31. Bonow RO, Lakatos E, Maron BJ, Epstein SE. Serial long-term assessment of the natural history of asymptomatic patients with chronic aortic regurgitation and normal left ventricular systolic function. Circulation. 1991; 84(4):1625-1635

32. Bonow RO, Picone AL, McIntosh CL, Jones M, Rosing DR, Maron BJ et al. Survival and functional results after valve replacement for aortic regurgitation from 1976 to 1983: impact of preoperative left ventricular function. Circulation. 1985; 72(6):1244-1256

33. Bonow RO, Rosing DR, McIntosh CL, Jones M, Maron BJ, Lan KK et al. The natural history of asymptomatic patients with aortic regurgitation and normal left ventricular function. Circulation. 1983; 68(3):509-517

34. Borer JS, Hochreiter C, Herrold EM, Supino P, Aschermann M, Wencker D et al. Prediction of indications for valve replacement among asymptomatic or minimally symptomatic patients with chronic aortic regurgitation and normal left ventricular performance. Circulation. 1998; 97(6):525-534

35. Brown ML, Pellikka PA, Schaff HV, Scott CG, Mullany CJ, Sundt TM et al. The benefits of early valve replacement in asymptomatic patients with severe aortic stenosis. Journal of Thoracic and Cardiovascular Surgery. 2008; 135(2):308-315

36. Calin A, Mateescu AD, Popescu AC, Bing R, Dweck MR, Popescu BA. Role of advanced left ventricular imaging in adults with aortic stenosis. Heart. 2020; 106(13):962-969

37. Calleja AM, Dommaraju S, Gaddam R, Cha S, Khandheria BK, Chaliki HP. Cardiac risk in patients aged >75 years with asymptomatic, severe aortic stenosis undergoing noncardiac surgery. American Journal of Cardiology. 2010; 105(8):1159-1163

38. Cameli M, Pastore MC, Righini FM, Mandoli GE, D'Ascenzi F, Lisi M et al. Prognostic value of left atrial strain in patients with moderate asymptomatic mitral regurgitation. International Journal of Cardiovascular Imaging. 2019; 35(9):1597-1604

39. Campo J, Tsoris A, Kruse J, Karim A, Andrei AC, Liu M et al. Prognosis of severe asymptomatic aortic stenosis with and without surgery. Annals of Thoracic Surgery. 2019; 108(1):74-79

40. Capoulade R, Magne J, Dulgheru R, Hachicha Z, Dumesnil JG, O'Connor K et al. Prognostic value of plasma B-type natriuretic peptide levels after exercise in patients with severe asymptomatic aortic stenosis. Heart. 2014; 100(20):1606-1612

41. Carabello BA. Indications for valve surgery in asymptomatic patients with aortic and mitral stenosis. Chest. 1995; 108(6):1678-1682

42. Carabello BA. Should severe aortic stenosis be operated on before symptom onset? Aortic valve replacement should be operated on before symptom onset. Circulation. 2012; 126(1):112-117

43. Carabello BA, Williams H, Gash AK, Kent R, Belber D, Maurer A et al. Hemodynamic predictors of outcome in patients undergoing valve replacement. Circulation. 1986; 74(6):1309-1316

44. Carasso S, Mutlak D, Lessick J, Reisner SA, Rakowski H, Agmon Y. Symptoms in severe aortic stenosis are associated with decreased compensatory circumferential myocardial mechanics. Journal of the American Society of Echocardiography. 2015; 28(2):218-225

45. Carstensen HG, Larsen LH, Hassager C, Kofoed KF, Jensen JS, Mogelvang R. Basal longitudinal strain predicts future aortic valve replacement in asymptomatic patients with aortic stenosis. European Heart Journal Cardiovascular Imaging. 2016; 17(3):283-292

46. Casaclang-Verzosa G, Malouf JF, Scott CG, Juracan EM, Nishimura RA, Pellikka PA. Does left atrial size predict mortality in asymptomatic patients with severe aortic stenosis? Echocardiography. 2010; 27(2):105-109

47. Casas-Rojo E, Fernandez-Golfin C, Moya-Mur JL, Gonzalez-Gomez A, Garcia-Martin A, Moran-Fernandez L et al. Area strain from 3D speckle-tracking echocardiography as an independent predictor of early symptoms or ventricular dysfunction in asymptomatic severe mitral regurgitation with preserved ejection fraction. International Journal of Cardiovascular Imaging. 2016; 32(8):1189-1198

48. Chaliki HP, Brown ML, Sundt TM, Tajik AJ. Timing of operation in asymptomatic severe aortic stenosis. Expert Review of Cardiovascular Therapy. 2007; 5(6):1065-1071

49. Chaliki HP, Mohty D, Avierinos JF, Scott CG, Schaff HV, Tajik AJ et al. Outcomes after aortic valve replacement in patients with severe aortic regurgitation and markedly reduced left ventricular function. Circulation. 2002; 106(21):2687-2693

50. Cheitlin MD. Asymptomatic adult patients with aortic stenosis: should they ever have aortic valve replacement? American Heart Hospital Journal. 2005; 3(4):243-246

51. Chenot F, Montant P, Vancraeynest D, Pasquet A, Gerber B, Noirhomme PH et al. Long-term clinical outcome of mitral valve repair in asymptomatic severe mitral regurgitation. European Journal of Cardio-Thoracic Surgery. 2009; 36(3):539-545

52. Cho IJ, Jeong H, Choi JY, Lee SE, Chang HJ. Prognostic implications of the left atrial volume index in patients with progressive mitral stenosis. Journal of Cardiovascular Imaging. 2019; 27(2):122-133

53. Cimadevilla C, Cueff C, Hekimian G, Dehoux M, Lepage L, Iung B et al. Prognostic value of B-type natriuretic peptide in elderly patients with aortic valve stenosis: the COFRASA-GENERAC study. Heart. 2013; 99(7):461-467

54. Cioffi G, Faggiano P, Vizzardi E, Tarantini L, Cramariuc D, Gerdts E et al. Prognostic effect of inappropriately high left ventricular mass in asymptomatic severe aortic stenosis. Heart. 2011; 97(4):301-307

55. Cioffi G, Mazzone C, Barbati G, Rossi A, Nistri S, Ognibeni F et al. Value of combined circumferential and longitudinal left ventricular systolic dysfunction to

predict adverse outcome in patients with asymptomatic aortic stenosis. Journal of Heart Valve Disease. 2016; 25(1):28-38

56. Clavel MA, Malouf J, Michelena HI, Suri RM, Jaffe AS, Mahoney DW et al. B-type natriuretic peptide clinical activation in aortic stenosis: impact on long-term survival. Journal of the American College of Cardiology. 2014; 63(19):2016-2025

57. Colli A, Bizzotto E, Besola L, Gregori D, Toto F, Manzan E et al. Risk stratification of severe aortic stenosis according to new guidelines: long term outcomes. Journal of Thoracic Disease. 2018; 10(10):5833-5841

58. Coutinho GF, Correia PM, Branco C, Antunes MJ. Long-term results of mitral valve surgery for degenerative anterior leaflet or bileaflet prolapse: analysis of negative factors for repair, early and late failures, and survival. European Journal of Cardio-Thoracic Surgery. 2016; 50(1):66-74

59. Coutinho GF, Garcia AL, Correia PM, Branco C, Antunes MJ. Long-term follow-up of asymptomatic or mildly symptomatic patients with severe degenerative mitral regurgitation and preserved left ventricular function. Journal of Thoracic and Cardiovascular Surgery. 2014; 148(6):2795-2801

60. Cramariuc D, Cioffi G, Rieck AE, Devereux RB, Staal EM, Ray S et al. Low-flow aortic stenosis in asymptomatic patients: valvular-arterial impedance and systolic function from the SEAS Substudy. JACC: Cardiovascular Imaging. 2009; 2(4):390-399

61. Dahl JS, Videbaek L, Poulsen MK, Rudbaek TR, Pellikka PA, Moller JE. Global strain in severe aortic valve stenosis: relation to clinical outcome after aortic valve replacement. Circulation: Cardiovascular Imaging. 2012; 5(5):613-620

62. Dal-Bianco JP, Khandheria BK, Mookadam F, Gentile F, Sengupta PP. Management of asymptomatic severe aortic stenosis. Journal of the American College of Cardiology. 2008; 52(16):1279-1292

63. De Jesus T, Alashry MM, Padang R, Pislaru SV, Nkomo VT, Pellikka PA et al. Intrinsic cardiac elastography in patients with primary mitral regurgitation: predictive role after mitral valve repair. European Heart Journal Cardiovascular Imaging. 2020; https://dx.doi.org/10.1093/ehjci/jeaa117

64. de Meester C, Gerber BL, Vancraeynest D, Pouleur AC, Noirhomme P, Pasquet A et al. Do guideline-based indications result in an outcome penalty for patients with severe aortic regurgitation? JACC: Cardiovascular Imaging. 2019; 12(11 Pt 1):2126-2138

65. de Meester C, Gerber BL, Vancraeynest D, Pouleur AC, Noirhomme P, Pasquet A et al. Early surgical intervention versus watchful waiting and outcomes for asymptomatic severe aortic regurgitation. Journal of Thoracic and Cardiovascular Surgery. 2015; 150(5):1100-1108

66. Delesalle G, Bohbot Y, Rusinaru D, Delpierre Q, Marechaux S, Tribouilloy C. Characteristics and prognosis of patients with moderate aortic stenosis and preserved left ventricular ejection fraction. Journal of the American Heart Association. 2019; 8(6):e011036

67. Detaint D, Messika-Zeitoun D, Avierinos J-F, Scott C, Chen H, Burnett Jr JC et al. B-type natriuretic peptide in organic mitral regurgitation: determinants and impact on outcome. Circulation. 2005; 111(18):2391-2397

68. Detaint D, Messika-Zeitoun D, Maalouf J, Tribouilloy C, Mahoney DW, Tajik AJ et al. Quantitative echocardiographic determinants of clinical outcome in asymptomatic

patients with aortic regurgitation: a prospective study. JACC: Cardiovascular Imaging. 2008; 1(1):1-11

69. Dorros G, Lewin RF, Stertzer SH, King JF, Waller BF, Myler RK et al. Percutaneous transluminal aortic valvuloplasty--the acute outcome and follow-up of 149 patients who underwent the double balloon technique. European Heart Journal. 1990; 11(5):429-440

70. Dujardin KS, Enriquez-Sarano M, Schaff HV, Bailey KR, Seward JB, Tajik AJ. Mortality and morbidity of aortic regurgitation in clinical practice. A long-term follow-up study. Circulation. 1999; 99(14):1851-1857

71. Dulgheru R, Weisz SH, Magne J, Lancellotti P. Risk stratification in asymptomatic aortic stenosis. European Cardiology. 2012; 8(2):120-124

72. Dupuis M, Mahjoub H, Clavel MA, Cote N, Toubal O, Tastet L et al. Forward left ventricular ejection fraction: A simple risk marker in patients with primary mitral regurgitation. Journal of the American Heart Association. 2017; 6(11):e006309

73. Egbe AC, Khan AR, Boler A, Said SM, Geske JB, Miranda WR et al. Role of diastolic function indices in the risk stratification of patients with mixed aortic valve disease. European Heart Journal Cardiovascular Imaging. 2018; 19(6):668-674

74. El Sabbagh A, Reddy YNV, Barros-Gomes S, Borlaug BA, Miranda WR, Pislaru SV et al. Low-gradient severe mitral stenosis: Hemodynamic profiles, clinical characteristics, and outcomes. Journal of the American Heart Association. 2019; 8(5):e010736

75. Enache R, Antonini-Canterin F, Piazza R, Popescu BA, Leiballi E, Marinigh R et al. CME: long-term outcome in asymptomatic patients with severe aortic regurgitation, normal left ventricular ejection fraction, and severe left ventricular dilatation. Echocardiography. 2010; 27(8):915-922

76. Enriquez-Sarano M, Avierinos JF, Messika-Zeitoun D, Detaint D, Capps M, Nkomo V et al. Quantitative determinants of the outcome of asymptomatic mitral regurgitation. New England Journal of Medicine. 2005; 352(9):875-883

77. Enriquez-Sarano M, Suri RM, Clavel MA, Mantovani F, Michelena HI, Pislaru S et al. Is there an outcome penalty linked to guideline-based indications for valvular surgery? Early and long-term analysis of patients with organic mitral regurgitation. Journal of Thoracic and Cardiovascular Surgery. 2015; 150(1):50-58

78. Enriquez-Sarano M, Tajik AJ, Schaff HV, Orszulak TA, Bailey KR, Frye RL. Echocardiographic prediction of survival after surgical correction of organic mitral regurgitation. Circulation. 1994; 90(2):830-837

79. Enriquez-Sarano M, Tajik AJ, Schaff HV, Orszulak TA, McGoon MD, Bailey KR et al. Echocardiographic prediction of left ventricular function after correction of mitral regurgitation: results and clinical implications. Journal of the American College of Cardiology. 1994; 24(6):1536-1543

80. Errichetti A, Greenberg JM, Gaasch WM. Is valve replacement indicated in asymptomatic patients with aortic stenosis or aortic regurgitation? Cardiovascular Clinics. 1990; 21(1):199-210; discussion 211-193

81. Ewe SH, Haeck ML, Ng AC, Witkowski TG, Auger D, Leong DP et al. Detection of subtle left ventricular systolic dysfunction in patients with significant aortic regurgitation and preserved left ventricular ejection fraction: speckle tracking echocardiographic analysis. European Heart Journal Cardiovascular Imaging. 2015; 16(9):992-999

82. Farre N, Gomez M, Molina L, Cladellas M, Ble M, Roqueta C et al. Prognostic value of NT-proBNP and an adapted monin score in patients with asymptomatic aortic stenosis. Revista Española de Cardiología. 2014; 67(1):52-57

83. Feuchtner GM, Muller S, Grander W, Alber HF, Bartel T, Friedrich GJ et al. Aortic valve calcification as quantified with multislice computed tomography predicts short-term clinical outcome in patients with asymptomatic aortic stenosis. Journal of Heart Valve Disease. 2006; 15(4):494-498

84. Flint N, Raschpichler M, Rader F, Shmueli H, Siegel RJ. Asymptomatic degenerative mitral regurgitation: A review. JAMA Cardiology. 2020; 5(3):346-355

85. Forman R, Firth BG, Barnard MS. Prognostic significance of preoperative left ventricular ejection fraction and valve lesion in patients with aortic valve replacement. American Journal of Cardiology. 1980; 45(6):1120-1125

86. Fries B, Liu D, Gaudron P, Hu K, Nordbeck P, Ertl G et al. Role of global longitudinal strain in the prediction of outcome in patients with severe aortic valve stenosis. American Journal of Cardiology. 2017; 120(4):640-647

87. Gaasch WH, Carroll JD, Levine HJ, Criscitiello MG. Chronic aortic regurgitation: prognostic value of left ventricular end-systolic dimension and end-diastolic radius/thickness ratio. Journal of the American College of Cardiology. 1983; 1(3):775-782

88. Gaasch WH, John RM, Aurigemma GP. Managing asymptomatic patients with chronic mitral regurgitation. Chest. 1995; 108(3):842-847

89. Gahl B, Celik M, Head SJ, Vanoverschelde JL, Pibarot P, Reardon MJ et al. Natural history of asymptomatic severe aortic stenosis and the association of early intervention with outcomes: A systematic review and meta-analysis. JAMA Cardiology. 2020; 5(10):1102–1112

90. Genereux P, Stone GW, O'Gara PT, Marquis-Gravel G, Redfors B, Giustino G et al. Natural history, diagnostic approaches, and therapeutic strategies for patients with asymptomatic severe aortic stenosis. Journal of the American College of Cardiology. 2016; 67(19):2263-2288

91. George SA, Prisco S, Onizuka T, Ortiz F, Malik U, Mbai M et al. An observational study of elderly veterans with initially asymptomatic severe aortic stenosis. Journal of Invasive Cardiology. 2019; 31(6):166-170

92. Gerber IL, Legget ME, West TM, Richards AM, Stewart RA. Usefulness of serial measurement of N-terminal pro-brain natriuretic peptide plasma levels in asymptomatic patients with aortic stenosis to predict symptomatic deterioration. American Journal of Cardiology. 2005; 95(7):898-901

93. Gerber IL, Stewart RA, Legget ME, West TM, French RL, Sutton TM et al. Increased plasma natriuretic peptide levels reflect symptom onset in aortic stenosis. Circulation. 2003; 107(14):1884-1890

94. Gerber W, Sanetra K, Drzewiecka-Gerber A, Jankowska-Sanetra J, Bochenek A, Zembala M et al. Long-term echocardiographic evaluation of asymptomatic patients undergoing minimally invasive valve repair for severe primary mitral regurgitation. Kardiologia Polska. 2020; 78(6):545-551

95. Gerdts E, Rossebo AB, Pedersen TR, Cioffi G, Lonnebakken MT, Cramariuc D et al. Relation of left ventricular mass to prognosis in initially asymptomatic mild to moderate aortic valve stenosis. Circulation Cardiovascular Imaging. 2015; 8(11):e003644; discussion e003644

96. Gillam LD, Marcoff L, Shames S. Timing of surgery in valvular heart disease: prophylactic surgery vs watchful waiting in the asymptomatic patient. Canadian Journal of Cardiology. 2014; 30(9):1035-1045

97. Giritharan S, Cagampang F, Torrens C, Salhiyyah K, Duggan S, Ohri S. Aortic stenosis prognostication in patients with type 2 diabetes: Protocol for testing and validation of a biomarker-derived scoring system. JMIR Research Protocols. 2019; 8(8):e13186

98. Gohlke-Barwolf C, Minners J, Jander N, Gerdts E, Wachtell K, Ray S et al. Natural history of mild and of moderate aortic stenosis-new insights from a large prospective European study. Current Problems in Cardiology. 2013; 38(9):365-409

99. Goldstone AB, Patrick WL, Cohen JE, Aribeana CN, Popat R, Woo YJ. Early surgical intervention or watchful waiting for the management of asymptomatic mitral regurgitation: a systematic review and meta-analysis. Annals of Cardiothoracic Surgery. 2015; 4(3):220-229

100. Gomez Perez M, Ble M, Cladellas M, Molina L, Vila J, Mas-Stachurska A et al. Combined use of tissue Doppler imaging and natriuretic peptides as prognostic marker in asymptomatic aortic stenosis. International Journal of Cardiology. 2017; 228:890-894

101. Gozdzik AT, Jasinski M, Gozdzik W. Echocardiographic evaluation of left ventricular strain in severe aortic stenosis with therapeutic implications and risk stratification. Advances in Clinical and Experimental Medicine. 2019; 28(9):1271-1279

102. Greves J, Rahimtoola SH, McAnulty JH, DeMots H, Clark DG, Greenberg B et al. Preoperative criteria predictive of late survival following valve replacement for severe aortic regurgitation. American Heart Journal. 1981; 101(3):300-308

103. Grigioni F, Enriquez-Sarano M, Ling LH, Bailey KR, Seward JB, Tajik AJ et al. Sudden death in mitral regurgitation due to flail leaflet. Journal of the American College of Cardiology. 1999; 34(7):2078-2085

104. Hachicha Z, Dumesnil JG, Bogaty P, Pibarot P. Paradoxical low-flow, low-gradient severe aortic stenosis despite preserved ejection fraction is associated with higher afterload and reduced survival. Circulation. 2007; 115(22):2856-2864

105. Hachicha Z, Dumesnil JG, Pibarot P. Usefulness of the valvuloarterial impedance to predict adverse outcome in asymptomatic aortic stenosis. Journal of the American College of Cardiology. 2009; 54(11):1003-1011

106. Henkel DM, Malouf JF, Connolly HM, Michelena HI, Sarano ME, Schaff HV et al. Asymptomatic left ventricular systolic dysfunction in patients with severe aortic stenosis: characteristics and outcomes. Journal of the American College of Cardiology. 2012; 60(22):2325-2329

107. Henri C, Dulgheru R, Magne J, Caballero L, Laaraibi S, Davin L et al. Impact of serial B-type natriuretic peptide changes for predicting outcome in asymptomatic patients with aortic stenosis. Canadian Journal of Cardiology. 2016; 32(2):183-189

108. Henry WL, Bonow RO, Rosing DR, Epstein SE. Observations on the optimum time for operative intervention for aortic regurgitation. II. Serial echocardiographic evaluation of asymptomatic patients. Circulation. 1980; 61(3):484-492

109. Hering D, Piper C, Horstkotte D. Influence of atypical symptoms and electrocardiographic signs of left ventricular hypertrophy or ST-segment/T-wave abnormalities on the natural history of otherwise asymptomatic adults with moderate

to severe aortic stenosis: preliminary communication. Journal of Heart Valve Disease. 2004; 13(2):182-187

110. Hristova-Antova E, Georgievska-Ismail L, Srbinovska E, Spiroska V, Hristova-Dimceva A, Zanteva-Naumoska M. Annual rate of progression of aortic-jet velocity and survival in cases of severe asymptomatic aortic stenosis. Prilozi Contributions. 2009; 30(1):91-104

111. Hu X, Jiang W, Li H, Yan G, Wang Y. Timing of valve repair for asymptomatic mitral regurgitation and preserved left ventricular function. Annals of Thoracic Surgery. 2020; https://dx.doi.org/10.1016/j.athoracsur.2020.06.017

112. Huded CP, Masri A, Kusunose K, Goodman AL, Grimm RA, Gillinov AM et al. Outcomes in asymptomatic severe aortic stenosis with preserved ejection fraction undergoing rest and treadmill stress echocardiography. Journal of the American Heart Association. 2018; 7(8):e007880

113. Ilardi F, Marchetta S, Martinez C, Sprynger M, Ancion A, Manganaro R et al. Impact of aortic stenosis on layer-specific longitudinal strain: relationship with symptoms and outcome European Heart Journal Cardiovascular Imaging. 2020; 21(4):408–416

114. Imai K, Okura H, Kume T, Yamada R, Miyamoto Y, Kawamoto T et al. C-Reactive protein predicts severity, progression, and prognosis of asymptomatic aortic valve stenosis. American Heart Journal. 2008; 156(4):713-718

115. Iung B, Baron G, Tornos P, Gohlke-Barwolf C, Butchart EG, Vahanian A. Valvular heart disease in the community: a European experience. Current Problems in Cardiology. 2007; 32(11):609-661

116. Iung B, Cormier B, Ducimetiere P, Porte JM, Nallet O, Michel PL et al. Functional results 5 years after successful percutaneous mitral commissurotomy in a series of 528 patients and analysis of predictive factors. Journal of the American College of Cardiology. 1996; 27(2):407-414

117. Izumo M, Takeuchi M, Seo Y, Yamashita E, Suzuki K, Ishizu T et al. Prognostic implications in patients with symptomatic aortic stenosis and preserved ejection fraction: Japanese multicenter aortic stenosis, retrospective (JUST-R) registry. Journal of Cardiology. 2017; 69(1):110-118

118. Jansen R, Kluin J, Ray SG, Chamuleau SAJ. MISSION: IMPOSSIBLE; The first randomized trial in asymptomatic patients with severe organic mitral valve regurgitation. Structural Heart. 2018; 2(5):382-385

119. Kaleschke G, Baumgartner H. Asymptomatic aortic stenosis: when to operate? Current Cardiology Reports. 2011; 13(3):220-225

120. Kanamori N, Taniguchi T, Morimoto T, Shiomi H, Ando K, Murata K et al. Asymptomatic versus symptomatic patients with severe aortic stenosis. Scientific Reports. 2018; 8:10080

121. Kanamori N, Taniguchi T, Morimoto T, Watanabe H, Shiomi H, Ando K et al. Prognostic impact of aortic valve area in conservatively managed patients with asymptomatic severe aortic stenosis with preserved ejection fraction. Journal of the American Heart Association. 2019; 8(3):e010198

122. Kang DH, Kim JH, Rim JH, Kim MJ, Yun SC, Song JM et al. Comparison of early surgery versus conventional treatment in asymptomatic severe mitral regurgitation. Circulation. 2009; 119(6):797-804

123. Kang DH, Lee CH, Kim DH, Yun SC, Song JM, Lee CW et al. Early percutaneous mitral commissurotomy vs. conventional management in asymptomatic moderate mitral stenosis. European Heart Journal. 2012; 33(12):1511-1517

124. Kang DH, Park SJ, Lee SA, Lee S, Kim DH, Kim HK et al. Early surgery or conservative care for asymptomatic aortic stenosis. New England Journal of Medicine. 2020; 382(2):111-119

125. Kang DH, Park SJ, Rim JH, Yun SC, Kim DH, Song JM et al. Early surgery versus conventional treatment in asymptomatic very severe aortic stenosis. Circulation. 2010; 121(13):1502-1509

126. Kang DH, Park SJ, Sun BJ, Cho EJ, Kim DH, Yun SC et al. Early surgery versus conventional treatment for asymptomatic severe mitral regurgitation: a propensity analysis. Journal of the American College of Cardiology. 2014; 63(22):2398-2407

127. Kearney LG, Lu K, Ord M, Patel SK, Profitis K, Matalanis G et al. Global longitudinal strain is a strong independent predictor of all-cause mortality in patients with aortic stenosis. European Heart Journal Cardiovascular Imaging. 2012; 13(10):827-833

128. Kelly TA, Rothbart RM, Cooper CM, Kaiser DL, Smucker ML, Gibson RS. Comparison of outcome of asymptomatic to symptomatic patients older than 20 years of age with valvular aortic stenosis. American Journal of Cardiology. 1988; 61(1):123-130

129. Kim HJ, Kim JB, Kim HR, Ju MH, Kang DY, Lee SA et al. Impact of valve replacement on long-term survival in asymptomatic patients with severe aortic stenosis. American Journal of Cardiology. 2019; 123(8):1321-1328

130. Kitai T, Honda S, Okada Y, Tani T, Kim K, Kaji S et al. Clinical outcomes in non-surgically managed patients with very severe versus severe aortic stenosis. Heart. 2011; 97(24):2029-2032

131. Kitai T, Taniguchi T, Morimoto T, Toyota T, Izumi C, Kaji S et al. Different clinical outcomes in patients with asymptomatic severe aortic stenosis according to the stage classification: Does the aortic valve area matter? International Journal of Cardiology. 2017; 228:244-252

132. Klaar U, Gabriel H, Bergler-Klein J, Pernicka E, Heger M, Mascherbauer J et al. Prognostic value of serial B-type natriuretic peptide measurement in asymptomatic organic mitral regurgitation. European Journal of Heart Failure. 2011; 13(2):163-169

133. Klodas E, Enriquez-Sarano M, Tajik AJ, Mullany CJ, Bailey KR, Seward JB. Optimizing timing of surgical correction in patients with severe aortic regurgitation: role of symptoms. Journal of the American College of Cardiology. 1997; 30(3):746-752

134. Kockova R, Linkova H, Hlubocka Z, Praveckova A, Polednova A, Sukupova L et al. New imaging markers of clinical outcome in asymptomatic patients with severe aortic regurgitation. Journal of Clinical Medicine. 2019; 8(10):1654

135. Krauss J, Pizarro R, Oberti PF, Falconi M, Cagide A. Prognostic implication of valvular lesion and left ventricular size in asymptomatic patients with chronic organic mitral regurgitation and normal left ventricular performance. American Heart Journal. 2006; 152(5):1004.e1001-1008

136. Kusunose K, Goodman A, Parikh R, Barr T, Agarwal S, Popovic ZB et al. Incremental prognostic value of left ventricular global longitudinal strain in patients with aortic stenosis and preserved ejection fraction. Circulation: Cardiovascular Imaging. 2014; 7(6):938-945

137. Lancellotti P, Donal E, Magne J, Moonen M, O'Connor K, Daubert JC et al. Risk stratification in asymptomatic moderate to severe aortic stenosis: the importance of the valvular, arterial and ventricular interplay. Heart. 2010; 96(17):1364-1371

138. Lancellotti P, Magne J, Donal E, Davin L, O'Connor K, Rosca M et al. Clinical outcome in asymptomatic severe aortic stenosis: insights from the new proposed aortic stenosis grading classification. Journal of the American College of Cardiology. 2012; 59(3):235-243

139. Lancellotti P, Magne J, Donal E, O'Connor K, Dulgheru R, Rosca M et al. Determinants and prognostic significance of exercise pulmonary hypertension in asymptomatic severe aortic stenosis. Circulation. 2012; 126(7):851-859

140. Lancellotti P, Magne J, Dulgheru R, Clavel MA, Donal E, Vannan MA et al. Outcomes of patients with asymptomatic aortic stenosis followed up in heart valve clinics. JAMA Cardiology. 2018; 3(11):1060-1068

141. Lancellotti P, Moonen M, Magne J, O'Connor K, Cosyns B, Attena E et al. Prognostic effect of long-axis left ventricular dysfunction and B-type natriuretic peptide levels in asymptomatic aortic stenosis. American Journal of Cardiology. 2010; 105(3):383-388

142. Laurenzano CS, Navarta DAC, Jorgi MFC, Mosto H, Casale AD. Prognostic value of longitudinal strain by velocity vector imaging in asymptomatic severe aortic stenosis with preserved ejection fraction. Revista Argentina de Cardiología. 2019; 87(6):408-413

143. Le Tourneau T, Messika-Zeitoun D, Russo A, Detaint D, Topilsky Y, Mahoney DW et al. Impact of left atrial volume on clinical outcome in organic mitral regurgitation. Journal of the American College of Cardiology. 2010; 56(7):570-578

144. Le Tourneau T, Pellikka PA, Brown ML, Malouf JF, Mahoney DW, Schaff HV et al. Clinical outcome of asymptomatic severe aortic stenosis with medical and surgical management: importance of STS score at diagnosis. Annals of Thoracic Surgery. 2010; 90(6):1876-1883

145. Le Tourneau T, Richardson M, Juthier F, Modine T, Fayad G, Polge AS et al. Echocardiography predictors and prognostic value of pulmonary artery systolic pressure in chronic organic mitral regurgitation. Heart. 2010; 96(16):1311-1317

146. Lee HF, Hsu LA, Chan YH, Wang CL, Chang CJ, Kuo CT. Prognostic value of global left ventricular strain for conservatively treated patients with symptomatic aortic stenosis. Journal of Cardiology. 2013; 62(5):301-306

147. Lee SY, Shim CY, Hong GR, Cho IJ, Chang HJ, Ha JW et al. Determinants and prognostic significance of symptomatic status in patients with moderately dysfunctional bicuspid aortic valves. PloS One. 2017; 12(1):e0169285

148. Levine HJ. Is valve surgery indicated in patients with severe mitral regurgitation even if they are asymptomatic? Cardiovascular Clinics. 1990; 21(1):161-170; discussion 171-163

149. Levy-Neuman S, Meledin V, Gandelman G, Goland S, Zilberman L, Edri O et al. The association between longitudinal strain at rest and stress and outcome in asymptomatic patients with moderate and severe aortic stenosis. Journal of the American Society of Echocardiography. 2019; 32(6):722-729

150. Lim P, Monin JL, Monchi M, Garot J, Pasquet A, Hittinger L et al. Predictors of outcome in patients with severe aortic stenosis and normal left ventricular function: role of B-type natriuretic peptide. European Heart Journal. 2004; 25(22):2048-2053

151. Lim WY, Ramasamy A, Lloyd G, Bhattacharyya S. Meta-analysis of the impact of intervention versus symptom-driven management in asymptomatic severe aortic stenosis. Heart. 2017; 103(4):268-272

152. Lindman BR, Clavel MA, Abu-Alhayja'a R, Cote N, Dagenais F, Novak E et al. Multimarker approach to identify patients with higher mortality and rehospitalization rate after surgical aortic valve replacement for aortic stenosis. JACC: Cardiovascular Interventions. 2018; 11(21):2172-2181

153. Lindman BR, Dweck MR, Lancellotti P, Genereux P, Pierard LA, O'Gara PT et al. Management of asymptomatic severe aortic stenosis: Evolving concepts in timing of valve replacement. JACC: Cardiovascular Imaging. 2020; 13(2 Pt 1):481-493

154. Ling LH, Enriquez-Sarano M, Seward JB, Tajik AJ, Schaff HV, Bailey KR et al. Clinical outcome of mitral regurgitation due to flail leaflet. New England Journal of Medicine. 1996; 335(19):1417-1423

155. Ma JI, Igata S, Strachan M, Nishimura M, Wong DJ, Raisinghani A et al. Predictive factors for progression of mitral regurgitation in asymptomatic patients with mitral valve prolapse. American Journal of Cardiology. 2019; 123(8):1309-1313

156. Maeda S, Taniguchi K, Toda K, Funatsu T, Kondoh H, Yokota T et al. Outcomes after aortic valve replacement for asymptomatic severe aortic regurgitation and normal ejection fraction. Seminars in Thoracic and Cardiovascular Surgery. 2019; 31(4):763-770

157. Maes F, Boulif J, Pierard S, de Meester C, Melchior J, Gerber B et al. Natural history of paradoxical low-gradient severe aortic stenosis. Circulation Cardiovascular Imaging. 2014; 7(4):714-722

158. Magne J, Cosyns B, Popescu BA, Carstensen HG, Dahl J, Desai MY et al. Distribution and prognostic significance of left ventricular global longitudinal strain in asymptomatic significant aortic stenosis: An individual participant data meta-analysis. JACC: Cardiovascular Imaging. 2019; 12(1):84-92

159. Magne J, Lancellotti P, Pierard LA. Exercise pulmonary hypertension in asymptomatic degenerative mitral regurgitation. Circulation. 2010; 122(1):33-41

160. Magne J, Mahjoub H, Dulgheru R, Pibarot P, Pierard LA, Lancellotti P. Left ventricular contractile reserve in asymptomatic primary mitral regurgitation. European Heart Journal. 2014; 35(24):1608-1616

161. Magne J, Mahjoub H, Pibarot P, Pirlet C, Pierard LA, Lancellotti P. Prognostic importance of exercise brain natriuretic peptide in asymptomatic degenerative mitral regurgitation. European Journal of Heart Failure. 2012; 14(11):1293-1302

162. Magne J, Mahjoub H, Pierard LA, O'Connor K, Pirlet C, Pibarot P et al. Prognostic importance of brain natriuretic peptide and left ventricular longitudinal function in asymptomatic degenerative mitral regurgitation. Heart. 2012; 98(7):584-591

163. Magne J, Szymanski C, Fournier A, Malaquin D, Avierinos JF, Tribouilloy C. Clinical and prognostic impact of a new left ventricular ejection index in primary mitral regurgitation because of mitral valve prolapse. Circulation: Cardiovascular Imaging. 2015; 8(9):e003036

164. Malouf J, Le Tourneau T, Pellikka P, Sundt TM, Scott C, Schaff HV et al. Aortic valve stenosis in community medical practice: determinants of outcome and implications for aortic valve replacement. Journal of Thoracic and Cardiovascular Surgery. 2012; 144(6):1421-1427

165. Marechaux S, Hachicha Z, Bellouin A, Dumesnil JG, Meimoun P, Pasquet A et al. Usefulness of exercise-stress echocardiography for risk stratification of true asymptomatic patients with aortic valve stenosis. European Heart Journal. 2010; 31(11):1390-1397

166. Marechaux S, Ringle A, Rusinaru D, Debry N, Bohbot Y, Tribouilloy C. Prognostic value of aortic valve area by doppler echocardiography in patients with severe asymptomatic aortic stenosis. Journal of the American Heart Association. 2016; 5(5):e003146

167. Marechaux S, Rusinaru D, Altes A, Pasquet A, Vanoverschelde JL, Tribouilloy C. Prognostic value of low flow in patients with high transvalvular gradient severe aortic stenosis and preserved left ventricular ejection fraction: A multicenter study. Circulation Cardiovascular Imaging. 2019; 12(10):e009299

168. Marwick TH, Scuffham PA, Hunink MG. Selection for early surgery in asymptomatic mitral regurgitation: a Markov model. International Journal of Cardiology. 2013; 165(2):266-272

169. Mateescu AD, Calin A, Beladan CC, Rosca M, Enache R, Baicus C et al. Left atrial dysfunction as an independent correlate of heart failure symptoms in patients with severe aortic stenosis and preserved left ventricular ejection fraction. Journal of the American Society of Echocardiography. 2019; 32(2):257-266

170. Mathieu T, Nguyen V, Cimadevilla C, Melissopoulou M, Codogno I, Verdonk C et al. Prognostic value of combination of hemodynamic parameters in asymptomatic aortic valve stenosis-The COFRASA/GENERAC study. Structural Heart. 2017; 1(1-2):75-80

171. Matos JD, Kiss JE, Locke AH, Goldberg RI, Mukamal K, Manning WJ. Relation of the mitral annular plane systolic excursion to risk for intervention in initially asymptomatic patients with aortic stenosis and preserved systolic function. American Journal of Cardiology. 2017; 120(11):2031-2034

172. Mentias A, Feng K, Alashi A, Rodriguez LL, Gillinov AM, Johnston DR et al. Long-term outcomes in patients with aortic regurgitation and preserved left ventricular ejection fraction. Journal of the American College of Cardiology. 2016; 68(20):2144-2153

173. Mentias A, Naji P, Gillinov AM, Rodriguez LL, Reed G, Mihaljevic T et al. Strain echocardiography and functional capacity in asymptomatic primary mitral regurgitation with preserved ejection fraction. Journal of the American College of Cardiology. 2016; 68(18):1974-1986

174. Mentias A, Patel K, Patel H, Gillinov AM, Rodriguez LL, Svensson LG et al. Prognostic utility of brain natriuretic peptide in asymptomatic patients with significant mitral regurgitation and preserved left ventricular ejection fraction. American Journal of Cardiology. 2016; 117(2):258-263

175. Messika-Zeitoun D, Bellamy M, Avierinos JF, Breen J, Eusemann C, Rossi A et al. Left atrial remodelling in mitral regurgitation--methodologic approach, physiological determinants, and outcome implications: a prospective quantitative Doppler-echocardiographic and electron beam-computed tomographic study. European Heart Journal. 2007; 28(14):1773-1781

176. Messika-Zeitoun D, Thomson H, Bellamy M, Scott C, Tribouilloy C, Dearani J et al. Medical and surgical outcome of tricuspid regurgitation caused by flail leaflets. Journal of Thoracic and Cardiovascular Surgery. 2004; 128(2):296-302

177. Michelena HI, Desjardins VA, Avierinos JF, Russo A, Nkomo VT, Sundt TM et al. Natural history of asymptomatic patients with normally functioning or minimally dysfunctional bicuspid aortic valve in the community. Circulation. 2008; 117(21):2776-2784

178. Miller LE, Miller VM, Acers LD. Asymptomatic severe aortic stenosis with left ventricular dysfunction: watchful waiting or valve replacement? Clinical Medicine & Research. 2013; 11(2):51-53

179. Minamino-Muta E, Kato T, Morimoto T, Taniguchi T, Ando K, Kanamori N et al. A risk prediction model in asymptomatic patients with severe aortic stenosis: CURRENT-AS risk score. European Heart Journal Quality of Care & Clinical Outcomes. 2020; 6(2):166-174

180. Miura S, Inoue K, Kumamaru H, Yamashita T, Hanyu M, Shirai S et al. Clinical impact of pathology-proven etiology of severely stenotic aortic valves on mid-term outcomes in patients undergoing surgical aortic valve replacement. PloS One. 2020; 15(3):e0229721

181. Miura S, Yamashita T, Hanyu M, Kumamaru H, Shirai S, Ando K. Propensity score-matched analysis of patients with severe aortic stenosis undergoing surgical aortic valve replacement. Open Heart. 2019; 6(1):e000992

182. Miyake M, Izumi C, Taniguchi T, Morimoto T, Amano M, Nishimura S et al. Early surgery vs. Surgery after watchful waiting for asymptomatic severe aortic stenosis. Circulation Journal. 2018; 82(10):2663-2671

183. Monin JL, Lancellotti P, Monchi M, Lim P, Weiss E, Pierard L et al. Risk score for predicting outcome in patients with asymptomatic aortic stenosis. Circulation. 2009; 120(1):69-75

184. Montant P, Chenot F, Robert A, Vancraeynest D, Pasquet A, Gerber B et al. Long-term survival in asymptomatic patients with severe degenerative mitral regurgitation: a propensity score-based comparison between an early surgical strategy and a conservative treatment approach. Journal of Thoracic and Cardiovascular Surgery. 2009; 138(6):1339-1348

185. Morimoto J, Hozumi T, Takemoto K, Wada T, Maniwa N, Kashiwagi M et al. Preoperative left atrial minimum volume as a surrogate marker of postoperative symptoms in senile patients with aortic stenosis who underwent surgical aortic valve replacement. Journal of Cardiology. 2019; 74(4):366-371

186. Nagata Y, Takeuchi M, Wu VC, Izumo M, Suzuki K, Sato K et al. Prognostic value of LV deformation parameters using 2D and 3D speckle-tracking echocardiography in asymptomatic patients with severe aortic stenosis and preserved LV ejection fraction. JACC: Cardiovascular Imaging. 2015; 8(3):235-245

187. Nakatsuma K, Taniguchi T, Morimoto T, Shiomi H, Ando K, Kanamori N et al. B-type natriuretic peptide in patients with asymptomatic severe aortic stenosis. Heart. 2019; 105(5):384-390

188. Nakatsuma K, Taniguchi T, Morimoto T, Shiomi H, Ando K, Kanamori N et al. Prognostic impact of peak aortic jet velocity in conservatively managed patients with severe aortic stenosis: An observation from the CURRENT AS registry. Journal of the American Heart Association. 2017; 6(7):e005524

189. Namisaki H, Nagata Y, Seo Y, Ishizu T, Izumo M, Akashi YJ et al. Symptomatic paradoxical low gradient severe aortic stenosis: A possible link to heart failure with preserved ejection fraction. Journal of Cardiology. 2019; 73(6):536-543

190. National Institute for Health and Care Excellence. Developing NICE guidelines: the manual [updated 2020]. London. National Institute for Health and Care Excellence, 2014. Available from: http://www.nice.org.uk/article/PMG20/chapter/1%20Introduction%20and%20overview

191. Nessmith MG, Fukuta H, Brucks S, Little WC. Usefulness of an elevated B-type natriuretic peptide in predicting survival in patients with aortic stenosis treated without surgery. American Journal of Cardiology. 2005; 96(10):1445-1448

192. Ng ACT, Prihadi EA, Antoni ML, Bertini M, Ewe SH, Ajmone Marsan N et al. Left ventricular global longitudinal strain is predictive of all-cause mortality independent of aortic stenosis severity and ejection fraction. European Heart Journal Cardiovascular Imaging. 2018; 19(8):859-867

193. Nguyen V, Cimadevilla C, Arangalage D, Dehoux M, Codogno I, Duval X et al. Determinants and prognostic value of B-type natriuretic peptide in patients with aortic valve stenosis. International Journal of Cardiology. 2017; 230:371-377

194. NHS England and NHS Improvement. 2018/19 National Cost Collection data. 2020. Available from: https://www.england.nhs.uk/national-cost-collection/#ncc1819 Last accessed: 01/12/2020.

195. Nistri S, Faggiano P, Olivotto I, Papesso B, Bordonali T, Vescovo G et al. Hemodynamic progression and outcome of asymptomatic aortic stenosis in primary care. American Journal of Cardiology. 2012; 109(5):718-723

196. O'Gara PT, Bonow RO. Thresholds for valve replacement in asymptomatic patients with aortic stenosis. JAMA Cardiology. 2018; 3(11):1068-1069

197. Ogutu P, Ahmed I, Dunning J. Should patients with asymptomatic severe mitral regurgitation with good left ventricular function undergo surgical repair? Interactive Cardiovascular and Thoracic Surgery. 2010; 10(2):299-305

198. Otto CM, Burwash IG, Legget ME, Munt BI, Fujioka M, Healy NL et al. Prospective study of asymptomatic valvular aortic stenosis. Clinical, echocardiographic, and exercise predictors of outcome. Circulation. 1997; 95(9):2262-2270

199. Owen A, Henein MY. Challenges in the management of severe asymptomatic aortic stenosis. European Journal of Cardio-Thoracic Surgery. 2011; 40(4):848-850

200. Pai RG, Kapoor N, Bansal RC, Varadarajan P. Malignant natural history of asymptomatic severe aortic stenosis: benefit of aortic valve replacement. Annals of Thoracic Surgery. 2006; 82(6):2116-2122

201. Pellikka PA, Nishimura RA, Bailey KR, Tajik AJ. The natural history of adults with asymptomatic, hemodynamically significant aortic stenosis. Journal of the American College of Cardiology. 1990; 15(5):1012-1017

202. Pellikka PA, Sarano ME, Nishimura RA, Malouf JF, Bailey KR, Scott CG et al. Outcome of 622 adults with asymptomatic, hemodynamically significant aortic stenosis during prolonged follow-up. Circulation. 2005; 111(24):3290-3295

203. Percy RF, Miller AB, Conetta DA. Usefulness of left ventricular wall stress at rest and after exercise for outcome prediction in asymptomatic aortic regurgitation. American Heart Journal. 1993; 125(1):151-155

204. Perera S, Wijesinghe N, Ly E, Devlin G, Pasupati S. Outcomes of patients with untreated severe aortic stenosis in real-world practice. New Zealand Medical Journal. 2011; 124(1345):40-48

205. Pierri H, Nussbacher A, Decourt LV, Medeiros C, Cattani A, Serro-Azul JB et al. Clinical predictors of prognosis in severe aortic stenosis in unoperated patients > or = 75 years of age. American Journal of Cardiology. 2000; 86(7):801-804, A810

206. Pineda AM, Kiefer TL. Asymptomatic severe aortic valve stenosis-when to intervene: A review of the literature, current trials, and guidelines. Current Cardiology Reports. 2018; 20:129

207. Piper C, Bergemann R, Schulte HD, Koerfer R, Horstkotte D. Can progression of valvar aortic stenosis be predicted accurately? Annals of Thoracic Surgery. 2003; 76(3):676-680; discussion 680

208. Pizarro R, Bazzino OO, Oberti PF, Falconi M, Achilli F, Arias A et al. Prospective validation of the prognostic usefulness of brain natriuretic peptide in asymptomatic patients with chronic severe mitral regurgitation. Journal of the American College of Cardiology. 2009; 54(12):1099-1106

209. Pizarro R, Bazzino OO, Oberti PF, Falconi ML, Arias AM, Krauss JG et al. Prospective validation of the prognostic usefulness of B-type natriuretic peptide in asymptomatic patients with chronic severe aortic regurgitation. Journal of the American College of Cardiology. 2011; 58(16):1705-1714

210. Potter E, Marwick TH. Assessment of left ventricular function by echocardiography: The case for routinely adding global longitudinal strain to ejection fraction. JACC: Cardiovascular Imaging. 2018; 11(2 Pt 1):260-274

211. Rajani R, Rimington H, Chambers J. B-type natriuretic peptide and tissue doppler for predicting symptoms on treadmill exercise in apparently asymptomatic aortic stenosis. Journal of Heart Valve Disease. 2009; 18(5):565-571

212. Ramos M, Quezada M, Ayala R, Gomez-Pavon FJ, Jaramillo J, Calderon-Dominguez M et al. Asymptomatic aortic stenosis in a geriatric population. The role of frailty and comorbidity in mortality. Revista Española de Cardiología. 2019; 24:https://doi.org/10.1016/j.rec.2019.1011.1006

213. Rashedi N, Popovic ZB, Stewart WJ, Marwick T. Outcomes of asymptomatic adults with combined aortic stenosis and regurgitation. Journal of the American Society of Echocardiography. 2014; 27(8):829-837

214. Recke SH, Marienhagen J, Feistel H, Platsch G, Bock E, von der Emde J. Electrocardiographic characteristics indicating a risk of irreversibly impaired myocardial function in chronic aortic regurgitation. International Journal of Cardiology. 1993; 42(2):129-138

215. Rezzoug N, Vaes B, Pasquet A, Gerber B, de Meester C, Van Pottelbergh G et al. Prevalence and prognostic impact of valve area-gradient patterns in patients >=80 years with moderate-to-severe aortic stenosis (from the prospective BELFRAIL study). American Journal of Cardiology. 2015; 116(6):925-932

216. Roseman DM, Magida MG, Lim WN. Natural history of asymptomatic and symptomatic mitral stenosis under medical management, 1949-1962. Journal of Chronic Diseases. 1965; 18:379-384

217. Rosen SE, Borer JS, Hochreiter C, Supino P, Roman MJ, Devereux RB et al. Natural history of the asymptomatic/minimally symptomatic patient with severe mitral regurgitation secondary to mitral valve prolapse and normal right and left ventricular performance. American Journal of Cardiology. 1994; 74(4):374-380

218. Rosenhek R. Watchful waiting for severe mitral regurgitation. Seminars in Thoracic and Cardiovascular Surgery. 2011; 23(3):203-208

219. Rosenhek R, Binder T, Porenta G, Lang I, Christ G, Schemper M et al. Predictors of outcome in severe, asymptomatic aortic stenosis. New England Journal of Medicine. 2000; 343(9):611-617

220. Rosenhek R, Klaar U, Schemper M, Scholten C, Heger M, Gabriel H et al. Mild and moderate aortic stenosis. Natural history and risk stratification by echocardiography. European Heart Journal. 2004; 25(3):199-205

221. Rosenhek R, Maurer G, Baumgartner H. Should early elective surgery be performed in patients with severe but asymptomatic aortic stenosis? European Heart Journal. 2002; 23(18):1417-1421

222. Rosenhek R, Rader F, Klaar U, Gabriel H, Krejc M, Kalbeck D et al. Outcome of watchful waiting in asymptomatic severe mitral regurgitation. Circulation. 2006; 113(18):2238-2244

223. Rosenhek R, Zilberszac R, Schemper M, Czerny M, Mundigler G, Graf S et al. Natural history of very severe aortic stenosis. Circulation. 2010; 121(1):151-156

224. Rubattu S, Volpe M. BNP level and post-transcatheter aortic valve replacement outcome: An intriguing J-shaped relationship. European Heart Journal. 2020; 41(8):970-972

225. Rusinaru D, Tribouilloy C, Grigioni F, Avierinos JF, Suri RM, Barbieri A et al. Left atrial size is a potent predictor of mortality in mitral regurgitation due to flail leaflets: results from a large international multicenter study. Circulation Cardiovascular Imaging. 2011; 4(5):473-481

226. Sa MPBO, Cavalcanti LRP, Escorel Neto ACA, Perazzo AM, Simonato M, Clavel MA et al. Early aortic valve replacement versus watchful waiting in asymptomatic severe aortic stenosis: A study-level meta-analysis. Structural Heart. 2019; 2(5):483-490

227. Saeed S, Mancia G, Rajani R, Parkin D, Chambers JB. Antihypertensive treatment with calcium channel blockers in patients with moderate or severe aortic stenosis: Relationship with all-cause mortality. International Journal of Cardiology. 2020; 298:122-125

228. Saeed S, Saeed N, Grigoryan K, Chowienczyk P, Chambers JB, Rajani R. Determinants and clinical significance of aortic stiffness in patients with moderate or severe aortic stenosis. International Journal of Cardiology. 2020; 315:99-104

229. Saito T, Muro T, Takeda H, Hyodo E, Ehara S, Nakamura Y et al. Prognostic value of aortic valve area index in asymptomatic patients with severe aortic stenosis. American Journal of Cardiology. 2012; 110(1):93-97

230. Salaun E, Casalta AC, Donal E, Bohbot Y, Galli E, Tribouilloy C et al. Apical four-chamber longitudinal left ventricular strain in patients with aortic stenosis and preserved left ventricular ejection fraction: analysis related with flow/gradient pattern and association with outcome. European Heart Journal Cardiovascular Imaging. 2018; 19(8):868-878

231. Samuels DA, Curfman GD, Friedlich AL, Buckley MJ, Austen WG. Valve replacement for aortic regurgitation: long-term follow-up with factors influencing the results. Circulation. 1979; 60(3):647-654

232. Sato K, Seo Y, Ishizu T, Takeuchi M, Izumo M, Suzuki K et al. Prognostic value of global longitudinal strain in paradoxical low-flow, low-gradient severe aortic stenosis with preserved ejection fraction. Circulation Journal. 2014; 78(11):2750-2759

233. Sharma V, Suri RM, Dearani JA, Burkhart HM, Park SJ, Joyce LD et al. Expanding relevance of aortic valve repair-is earlier operation indicated? Journal of Thoracic and Cardiovascular Surgery. 2014; 147(1):100-107

234. Shibayama K, Daimon M, Watanabe H, Kawata T, Miyazaki S, Morimoto-Ichikawa R et al. Significance of coronary artery disease and left ventricular afterload in unoperated asymptomatic aortic stenosis. Circulation Journal. 2016; 80(2):519-525

235. Shirai S, Taniguchi T, Morimoto T, Ando K, Korai K, Minakata K et al. Five-year clinical outcome of asymptomatic vs. Symptomatic severe aortic stenosis after aortic valve replacement. Circulation Journal. 2017; 81(4):485-494

236. Sia CH, Ho JS, Chua JJ, Tan BY, Ngiam NJ, Chew N et al. Comparison of clinical and echocardiographic features of asymptomatic patients with stenotic bicuspid versus tricuspid aortic valves. American Journal of Cardiology. 2020; 128:210-215

237. Siemienczuk D, Greenberg B, Morris C, Massie B, Wilson RA, Topic N et al. Chronic aortic insufficiency: factors associated with progression to aortic valve replacement. Annals of Internal Medicine. 1989; 110(8):587-592

238. Sinha SK, Garg S, Thakur R, Krishna V, Singh K, Sachan M et al. Prognostic importance of exercise brain natriuretic peptide in asymptomatic chronic organic severe mitral regurgitation: An observational study. Journal of Clinical Medicine Research. 2016; 8(11):797-804

239. Stahle E, Kvidal P, Nystrom SO, Bergstrom R. Long-term relative survival after primary heart valve replacement. European Journal of Cardio-Thoracic Surgery. 1997; 11(1):81-91

240. Stewart RA, Kerr AJ, Whalley GA, Legget ME, Zeng I, Williams MJ et al. Left ventricular systolic and diastolic function assessed by tissue Doppler imaging and outcome in asymptomatic aortic stenosis. European Heart Journal. 2010; 31(18):2216-2222

241. Sun BJ, Oh JK, Lee SH, Jang JY, Lee JH, Lee S et al. Mid-term clinical outcomes in a cohort of asymptomatic or mildly symptomatic korean patients with bicuspid aortic valve in a tertiary referral hospital. Journal of Cardiovascular Imaging. 2019; 27(2):105-118

242. Suzuki A, Tajiri K, Ishizu T, Nakayama M, Hoshi T, Suzuki S et al. Effect of asymptomatic severe aortic stenosis on outcomes of individuals aged 80 and older. Journal of the American Geriatrics Society. 2018; 66(9):1800-1804

243. Takeda S, Rimington H, Chambers J. Prediction of symptom-onset in aortic stenosis: a comparison of pressure drop/flow slope and haemodynamic measures at rest. International Journal of Cardiology. 2001; 81(2-3):131-137; discussion 138-139

244. Taniguchi T, Morimoto T, Shiomi H, Ando K, Kanamori N, Murata K et al. Sudden death in patients with severe aortic stenosis: Observations from the CURRENT AS registry. Journal of the American Heart Association. 2018; 7(11):e008397

245. Taniguchi T, Morimoto T, Shiomi H, Ando K, Kanamori N, Murata K et al. Initial surgical versus conservative strategies in patients with asymptomatic severe aortic stenosis. Journal of the American College of Cardiology. 2015; 66(25):2827-2838

246. Taniguchi T, Morimoto T, Takeji Y, Kato T, Kimura T, Investigators CAr. Contemporary issues in severe aortic stenosis: review of current and future strategies from the Contemporary Outcomes after Surgery and Medical Treatment in Patients with Severe Aortic Stenosis registry. Heart. 2020; 106(11):802-809

247. Taniguchi T, Shiomi H, Kosuge M, Morimoto T, Nakatsuma K, Nishiga M et al. Prognostic significance of ST-segment elevation in leads V1-2 in patients with severe aortic stenosis. Circulation Journal. 2016; 80(2):526-534

248. Tarasoutchi F, Grinberg M, Filho JP, Izaki M, Cardoso LF, Pomerantezeff P et al. Symptoms, left ventricular function, and timing of valve replacement surgery in patients with aortic regurgitation. American Heart Journal. 1999; 138(3 Pt 1):477-485

249. Tarasoutchi F, Grinberg M, Spina GS, Sampaio RO, Cardoso L, Rossi EG et al. Ten-year clinical laboratory follow-up after application of a symptom-based therapeutic strategy to patients with severe chronic aortic regurgitation of predominant rheumatic etiology. Journal of the American College of Cardiology. 2003; 41(8):1316-1324

250. Tastet L, Tribouilloy C, Marechaux S, Vollema EM, Delgado V, Salaun E et al. Staging cardiac damage in patients with asymptomatic aortic valve stenosis. Journal of the American College of Cardiology. 2019; 74(4):550-563

251. Teraguchi I, Hozumi T, Emori H, Takemoto K, Fujita S, Wada T et al. Prognostic value of tissue-tracking mitral annular displacement by speckle-tracking echocardiography in asymptomatic aortic stenosis patients with preserved left ventricular ejection fraction. Journal of Echocardiography. 2020; 24:https://doi.org/10.1007/s12574-12020-00490-w

252. Thakker P, Husaini M, Thangam M, Lindman B, Maniar H, Quader N et al. Transcatheter aortic valve replacement (TAVR) in patients with paradoxical low-flow low-gradient aortic stenosis. Structural Heart. 2020; 4(4):312-319

253. Thellier N, Altes A, Appert L, Binda C, Leman B, Marsou W et al. Prognostic importance of left ventricular global longitudinal strain in patients with severe aortic stenosis and preserved ejection fraction. Journal of the American Society of Echocardiography. 2020; https://doi.org/10.1016/j.echo.2020.07.002

254. Thomassen HK, Cioffi G, Gerdts E, Einarsen E, Midtbo HB, Mancusi C et al. Echocardiographic aortic valve calcification and outcomes in women and men with aortic stenosis. Heart. 2017; 103(20):1619-1624

255. Thompson R, Ross I, McHaffie D, Leslie P, Easthope R, Elmes R. Left ventricular function in asymptomatic patients with severe aortic regurgitation: relation to clinical parameters and exercise performance. Clinical Cardiology. 1982; 5(10):523-530

256. Tietge WJ, de Heer LM, van Hessen MWJ, Jansen R, Bots ML, van Gilst W et al. Early mitral valve repair versus watchful waiting in patients with severe asymptomatic organic mitral regurgitation; rationale and design of the Dutch AMR trial, a multicenter, randomised trial. Netherlands Heart Journal. 2012; 20(3):94-101

257. Todaro MC, Carerj S, Khandheria B, Cusma-Piccione M, La Carrubba S, Antonini-Canterin F et al. Usefulness of atrial function for risk stratification in asymptomatic severe aortic stenosis. Journal of Cardiology. 2016; 67(1):71-79

258. Tomsic A, Hiemstra YL, van Hout FMA, van Brakel TJ, Versteegh MIM, Marsan NA et al. Long-term results of mitral valve repair for severe mitral regurgitation in asymptomatic patients. Journal of Cardiology. 2018; 72(6):473-479

259. Tornos MP, Olona M, Permanyer-Miralda G, Herrejon MP, Camprecios M, Evangelista A et al. Clinical outcome of severe asymptomatic chronic aortic regurgitation: a long-term prospective follow-up study. American Heart Journal. 1995; 130(2):333-339

260. Tornos MP, Permanyer-Miralda G, Evangelista A, Worner F, Candell J, Garcia-del-Castillo H et al. Clinical evaluation of a prospective protocol for the timing of surgery in chronic aortic regurgitation. American Heart Journal. 1990; 120(3):649-657

261. Tornos P, Sambola A, Permanyer-Miralda G, Evangelista A, Gomez Z, Soler-Soler J. Long-term outcome of surgically treated aortic regurgitation: influence of guideline adherence toward early surgery. Journal of the American College of Cardiology. 2006; 47(5):1012-1017

262. Tribouilloy C, Grigioni F, Avierinos JF, Barbieri A, Rusinaru D, Szymanski C et al. Survival implication of left ventricular end-systolic diameter in mitral regurgitation due to flail leaflets a long-term follow-up multicenter study. Journal of the American College of Cardiology. 2009; 54(21):1961-1968

263. Tribouilloy C, Rusinaru D, Szymanski C, Mezghani S, Fournier A, Levy F et al. Predicting left ventricular dysfunction after valve repair for mitral regurgitation due to leaflet prolapse: additive value of left ventricular end-systolic dimension to ejection fraction. European Journal of Echocardiography. 2011; 12(9):702-710

264. Tribouilloy CM, Enriquez-Sarano M, Schaff HV, Orszulak TA, Bailey KR, Tajik AJ et al. Impact of preoperative symptoms on survival after surgical correction of organic mitral regurgitation: rationale for optimizing surgical indications. Circulation. 1999; 99(3):400-405

265. Turina J, Turina M, Rothlin M, Krayenbuehl HP. Improved late survival in patients with chronic aortic regurgitation by earlier operation. Circulation. 1984; 70(3 Pt 2):I147-152

266. Vaquette B, Corbineau H, Laurent M, Lelong B, Langanay T, de Place C et al. Valve replacement in patients with critical aortic stenosis and depressed left ventricular function: predictors of operative risk, left ventricular function recovery, and long term outcome. Heart. 2005; 91(10):1324-1329

267. Varadarajan P, Kapoor N, Bansal RC, Pai RG. Clinical profile and natural history of 453 nonsurgically managed patients with severe aortic stenosis. Annals of Thoracic Surgery. 2006; 82(6):2111-2115

268. Verseckaite R, Mizariene V, Montvilaite A, Auguste I, Bieseviciene M, Laukaitiene J et al. The predictive value of left ventricular myocardium mechanics evaluation in asymptomatic patients with aortic regurgitation and preserved left ventricular ejection fraction. A long-term speckle-tracking echocardiographic study. Echocardiography. 2018; 35(9):1277-1288

269. Vollema EM, Sugimoto T, Shen M, Tastet L, Ng ACT, Abou R et al. Association of left ventricular global longitudinal strain with asymptomatic severe aortic stenosis: Natural course and prognostic value. JAMA Cardiology. 2018; 3(9):839-847

270. Wang Y, Jiang W, Liu J, Li G, Liu Y, Hu X et al. Early surgery versus conventional treatment for asymptomatic severe aortic regurgitation with normal ejection fraction and left ventricular dilatation. European Journal of Cardio-Thoracic Surgery. 2017; 52(1):118-124

271. Wang Y, Shi J, Li F, Wang Y, Dong N. Aortic valve replacement for severe aortic regurgitation in asymptomatic patients with normal ejection fraction and severe left ventricular dilatation. Interactive Cardiovascular and Thoracic Surgery. 2016; 22(4):425-430

272. Wilson RA, McDonald RW, Bristow JD, Cheitlin M, Nauman D, Massie B et al. Correlates of aortic distensibility in chronic aortic regurgitation and relation to

progression to surgery. Journal of the American College of Cardiology. 1992; 19(4):733-738

273. Wisenbaugh T, Booth D, DeMaria A, Nissen S, Waters J. Relationship of contractile state to ejection performance in patients with chronic aortic valve disease. Circulation. 1986; 73(1):47-53

274. Wisenbaugh T, Skudicky D, Sareli P. Prediction of outcome after valve replacement for rheumatic mitral regurgitation in the era of chordal preservation. Circulation. 1994; 89(1):191-197

275. Wu VC, Takeuchi M, Nagata Y, Izumo M, Akashi YJ, Lin FC et al. Prognostic value of area of calcified aortic valve by 2-dimensional echocardiography in asymptomatic severe aortic stenosis patients with preserved left ventricular ejection fraction. Medicine. 2018; 97(12):e0246

276. Yang LT, Liu YW, Shih JY, Li YH, Tsai LM, Luo CY et al. Predictive value of left atrial deformation on prognosis in severe primary mitral regurgitation. Journal of the American Society of Echocardiography. 2015; 28(11):1309-1317.e1304

277. Yingchoncharoen T, Gibby C, Rodriguez LL, Grimm RA, Marwick TH. Association of myocardial deformation with outcome in asymptomatic aortic stenosis with normal ejection fraction. Circulation Cardiovascular Imaging. 2012; 5(6):719-725

278. Yousof AM, Mohammed MM, Shuhaiber H, Cherian G. Chronic severe aortic regurgitation: a prospective follow-up of 60 asymptomatic patients. American Heart Journal. 1988; 116(5 Pt 1):1262-1267

279. Zhao Y, Owen A, Henein M. Early valve replacement for aortic stenosis irrespective of symptoms results in better clinical survival: a meta-analysis of the current evidence. International Journal of Cardiology. 2013; 168(4):3560-3563

280. Zhou T, Li J, Lai H, Zhu K, Sun Y, Ding W et al. Benefits of early surgery on clinical outcomes after degenerative mitral valve repair. Annals of Thoracic Surgery. 2018; 106(4):1063-1070

281. Zilberszac R, Gabriel H, Schemper M, Laufer G, Maurer G, Rosenhek R. Asymptomatic severe aortic stenosis in the elderly. JACC: Cardiovascular Imaging. 2017; 10(1):43-50

282. Zito C, Salvia J, Cusma-Piccione M, Antonini-Canterin F, Lentini S, Oreto G et al. Prognostic significance of valvuloarterial impedance and left ventricular longitudinal function in asymptomatic severe aortic stenosis involving three-cuspid valves. American Journal of Cardiology. 2011; 108(10):1463-1469

283. Zlotnick DM, Ouellette ML, Malenka DJ, DeSimone JP, Leavitt BJ, Helm RE et al. Effect of preoperative pulmonary hypertension on outcomes in patients with severe aortic stenosis following surgical aortic valve replacement. American Journal of Cardiology. 2013; 112(10):1635-1640

Appendices

Appendix A: Review protocols

Table 20: Review protocol: indications for intervention in asymptomatic, severe HVD

ID	Field	Content
0.	PROSPERO registration number	CRD42019158255
1.	Review title	What are the indications that interventions should be offered to adults with asymptomatic, severe heart valve disease?
2.	Review question	What are the indications that interventions should be offered to adults with asymptomatic, severe heart valve disease?
3.	Objective	To identify the indications for intervention in people with asymptomatic, severe heart valve disease
4.	Searches	The following databases will be searched: Cochrane Database of Systematic Reviews (CDSR) Embase MEDLINE Searches will be restricted by: English language Human studies Letters and comments are excluded Other searches: Inclusion lists of systematic reviews will be checked by the reviewer The searches may be re-run 6 weeks before 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	Adults aged 18 years and over with diagnosed severe heart valve disease that is asymptomatic, stratified by the type of heart valve disease as follows: aortic [including bicuspid] stenosis aortic regurgitation mitral stenosis mitral regurgitation tricuspid 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. Exclusion: Children (aged <18 years).

ID	Field	Content
		Adults with congenital heart disease (excluding bicuspid aortic valves). Tricuspid stenosis and pulmonary valve disease. Adults with previous intervention for HVD (surgical or transcatheter). Secondary heart valve disease because it does not occur in the asymptomatic group 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.	Indicators for intervention	In those with severe, asymptomatic heart valve disease the following parameters will be assessed according to type of HVD. Functional and anatomical parameters refer to measurements from echocardiography: 1. Mitral regurgitation Primary mitral regurgitation left ventricular systolic function based on ejection fraction <50% or <60% Left ventricular systolic function based on global longitudinal strain (absolute value <20%; may be reported as in the range 0 to -20% or >-20%) left ventricular end systolic diameter ≥40mm or ≥45mm peak systolic pulmonary artery pressure >50mmHg left atrial dimensions (volume / volume index) ≥60 mL/m2 BSA Repairability/valve morphology: posterior leaflet prolapse, anterior leaflet prolapse, bileaflet prolapse flail valve / ruptured chordae development of atrial fibrillation BNP increase at serial measurements (without other explanation) 2. Aortic stenosis Peak velocity >5m/sec or >5.5m/sec Rate of progression of velocity >0.3m/sec/year Aortic valve area <0.6cm2 left ventricular systolic function based on ejection fraction <50% or <60% left ventricular systolic function based on global longitudinal strain absolute value <20%; may be reported as 0 to -20% or >-20%) parameters of diastolic function / indicators of left atrial filling pressure (E/e'>14) systolic pulmonary artery pressure >60mmHg (without other explanation) BNP increase at serial measurements (without other explanation) 3. Aortic regurgitation left ventricular systolic function based on ejection fraction <50% left ventricular systolic function based on global longitudinal strain absolute value <20%; may be reported as 0 to -20% or >-20%) left ventricular dimensions end diastolic diameter, LVEDD >70mm

ID	Field	Content
		end systolic diameter, LVESD >50mm end diastolic volume, LVESD >25mm/m2 BSA BNP increase at serial measurements (without other explanation) 4. Mitral stenosis mitral valve area <1cm2 or <1.5cm2 systolic pulmonary artery pressure >50mmHg mitral valve gradient mean gradient >5mmHg at rest reduced right ventricular function (tricuspid annular plane systolic excursion [TAPSE] <17) mitral valve morphology – deemed suitable for transcatheter balloon valvotomy BNP increase at serial measurements (without other explanation) 5. Tricuspid regurgitation (isolated) reduced right ventricular systolic function – no thresholds increasing right ventricular dimensions – no thresholds (dilated – mild, moderate, severe) BNP increase at serial measurements (without other explanation) Valve morphology – suitable for repair If studies report combinations of these factors together and how effective these are – they will be included
8.	Confounding factors	Risk scores (e.g. EuroScore I or II, STS score) Age Sex Renal impairment Extra cardiac arteriopathy/ Peripheral arterial disease/ Cerebrovascular disease Previous cardiac surgery Chronic lung disease Diabetes Hypertension Prior MI Active endocarditis Frailty scores (e.g. CSHA, Katz score)
9.	Types of study to be included	Prospective and retrospective cohort studies Systematic reviews of the above If no cohort studies are identified case control studies with multivariate analysis will be included. Studies with univariate analysis only will be excluded.
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 study design or analysis Non-English language studies

ID	Field	Content
		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	N/A
12.	Primary outcomes (critical outcomes)	Indication for intervention based on prognosis for the following without intervention: Mortality (≥12 months) Hospital admission for heart failure (≥12 months) Reduced cardiac function (echo parameters – LVEF) Indication for intervention based on pre-operative predictors of the following post-operative outcomes: Mortality (≥12 months) Hospital admission for heart failure (≥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 latest reported time point.
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). Summary evidence tables will be produced including information on: study setting; study population and participant demographics and baseline characteristics; details of the prognostic factors; study methodology' recruitment and missing data rates; outcomes and times of measurement; critical appraisal ratings. MS Excel will be used for data extraction and critical appraisal for health economic studies.
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.

ID	Field	Content	
16.	Strategy for data synthesis	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 bias will be assessed if there are 5 or more studies for a given outcome. 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.	
17.	Analysis of sub-groups	Groups that will be analysed separately (strata): Population: Stratified by the presence or absence of symptoms and the type of heart valve disease as follows: aortic [including bicuspid] stenosis aortic regurgitation mitral stenosis mitral regurgitation tricuspid regurgitation Subgroups that will be investigated if heterogeneity is present: Age (<75/≥75 years) Single vs multiple valve disease Co-morbid cardiac abnormalities Studies will be assigned to different subgroups using a threshold of 75% - for example, a study in which 80% of the population have single valve disease and 20% have multiple valve disease would be assigned to the single valve disease group when subgrouping for this factor.	
18.	Type and method of review	☐	Intervention
		☐	Diagnostic
		☒	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery
		☐	Other (please specify)
19.	Language	English	

ID	Field	Content		
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		

ID	Field	Content	
		the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10122	
29.	Other registration details	N/A	
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; Biological heart valve; Heart valve disease; Heart valve repair; Heart valve replacement; Intervention; Mechanical heart valve; Mitral regurgitation; Mitral stenosis; Surgical valve replacement; Transcatheter valve replacement; 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

2 **Table 21: 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).[190] **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 7 - indications for specialist referral following echocardiography

This literature search strategy was used for the following review:

- What are the indications that interventions should be offered to adults with asymptomatic, severe heart valve disease?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[190]

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

This prognostic search was constructed using one following approaches:

- Population AND Prognostic/risk factor terms

Table 22: 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
The Cochrane Library (Wiley)	Cochrane Reviews to 2020 Issue 10 of 12	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.	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/20-26
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.	Asymptomatic Diseases/
33.	asymptomatic.ti,ab.
34.	(symptom* adj3 (absent or non or none or no or missed or missing or unseen or "not apparent" or clinically silent or subclinical)).ti,ab.
35.	or/32-34
36.	31 and 35

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/17-24
26.	9 not 25
27.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
28.	26 not 27
29.	limit 28 to English language
30.	asymptomatic disease/
31.	asymptomatic.ti,ab.
32.	(symptom* adj3 (absent or non or none or no or missed or missing or unseen or "not apparent" or clinically silent or subclinical)).ti,ab.
33.	or/30-32

34.	29 and 33

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Heart Valve Diseases] explode all trees
#2.	MeSH descriptor: [Heart Valves] explode all trees
#3.	((primary or secondary) NEXT valv* disease*):ti,ab
#4.	((valv* or flap* or leaflet*) near/1 (heart or cardiac) NEXT (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*) NEXT (valv* or flap* or leaflet*) NEXT (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*) NEAR/3 (prolapse or regurgitation or stenos?s or atresia or insufficienc*)):ti,ab
#7.	MeSH descriptor: [Heart Murmurs] explode all trees
#8.	((heart or cardiac) NEXT murmur*):ti,ab
#9.	(or #1-#8)
#10.	MeSH descriptor: [Asymptomatic Diseases] this term only
#11.	asymptomatic:ti,ab
#12.	(symptom* near/3 (absent or non or none or no or missed or missing or unseen or subclinical)):ti,ab
#13.	"not apparent":ti,ab
#14.	"clinically silent":ti,ab
#15.	(or #10-#14)
#16.	#9 and #15

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 23: 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**

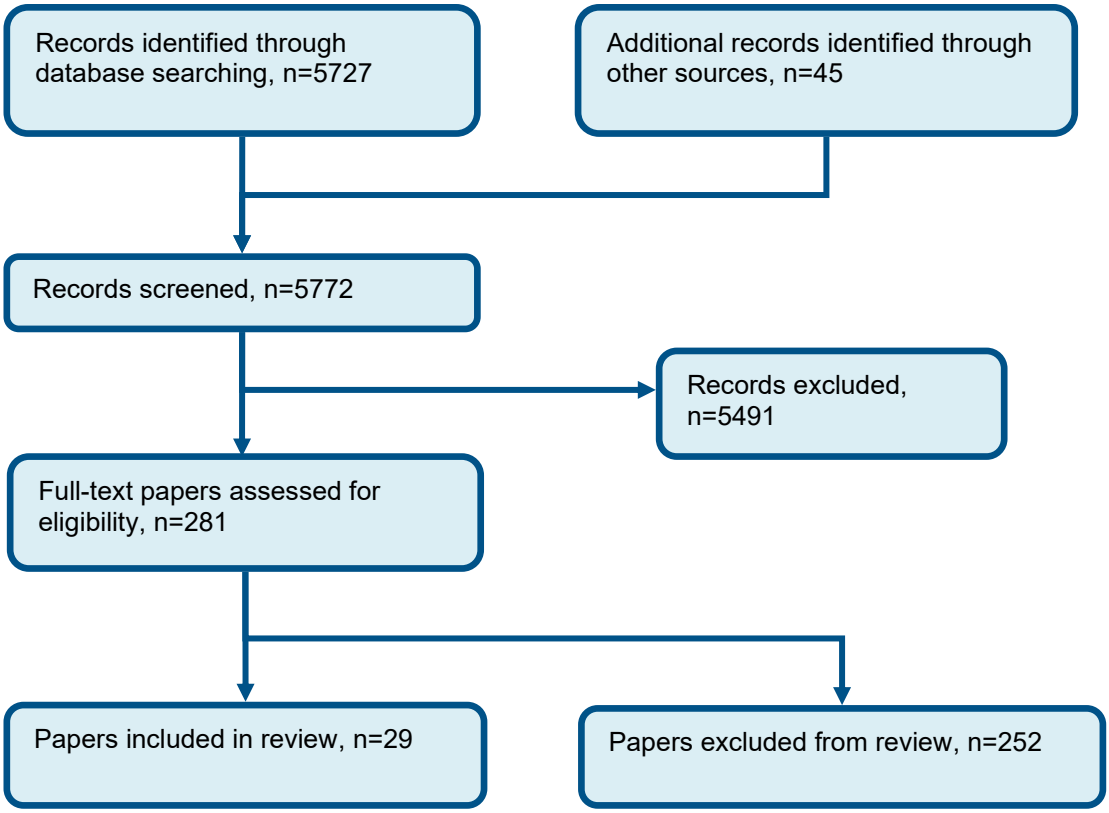
#1.	MeSH DESCRIPTOR Heart Valve Diseases EXPLODE ALL TREES
#2.	MeSH DESCRIPTOR Heart Valves EXPLODE ALL TREES
#3.	(((primary or secondary) adj Valv* adj disease*))
#4.	(((valv* or flap* or leaflet*) adj (heart or cardiac) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* 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: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of indications for intervention in asymptomatic, severe HVD



Appendix D: Clinical evidence tables

D.1 Aortic stenosis

Reference	Bohbot 2017[30]
Study type and analysis	Retrospective chart review of patients identified between 2000 and 2015 Multivariable Cox proportional hazards model.
Number of participants and characteristics	N=1140 (subgroup with no or minimal symptoms = 558) Vmax groups in NYHA 1-2 group: 4-4.49 m/s n=229 <5.0m/s n=389 4.50-4.99 m/s n=160 ≥5.0 m/s n=169 5-5.49 m/s n=104 ≥5.5 m/s n=65 **Inclusion criteria:** Aged ≥18 years, diagnosed with severe AS (defined as AVA ≤1 cm^2 or AVA normalized to body surface area [BSA] ≤0.6 cm^2/m^2, and Vmax ≥4 m/s). No or minimal symptoms. Symptoms were ascertained by each patient's cardiologist. Patients with atypical chest pain and elderly patients with minimal dyspnoea not clearly related to AS were considered to be minimally symptomatic. **Exclusion criteria:** (1) individuals with more than mild aortic and mitral regurgitation; (2) patients with prosthetic valves, congenital heart disease (with the exception of bicuspid aortic valves), supravalvular or subvalvular AS, or dynamic left ventricular (LV) outflow tract obstruction, and (3) individuals who declined to participate in the study. Demographic details (for NYHA 1-2 group) • Mean (SD) age: Vmax 4-4.49 m/s: 74 (11) years Vmax 4.50-4.99 m/s: 73 (12) years Vmax 5-5.49 m/s: 72 (12) years Vmax ≥5.5 m/s: 72 (12) years

Reference	Bohbot 2017[30]
	• Sex: 51% male • Single vs multiple valve disease: NA • Co-morbid cardiac abnormalities: **Coronary artery disease** / **Prior atrial fibrillation** Vmax 4-4.49 m/s: 41.9% / 26.2% Vmax 4.50-4.99 m/s: 46.9% / 25.6% Vmax 5-5.49 m/s: 47.1% / 27.9% Vmax ≥5.5 m/s: 44.6% / 13.8% **Population source:** Prospectively identified and included in an electronic database from 2 French university hospital echo labs
Prognostic variables	Vmax 4-4.49 m/s (reference group) Vmax 4.50-4.99 m/s Vmax 5-5.49 m/s Vmax ≥5.5 m/s Vmax <5.0 m/s (reference group) Vmax ≥5.0 m/s
Confounders	The following covariates considered to have a potential prognostic impact (on the basis of epidemiological data) were included: age, sex, BSA, hypertension, New York Heart Association class, coronary artery disease, history of atrial fibrillation, comorbidity index, LVEF, and aortic valve surgery (treated as a time-dependent covariate).
Outcomes and effect sizes	**All-cause mortality (analysis 1, multiple thresholds)** HR (95% CI) 0.80 (0.52–1.22) for Vmax 4.50-4.99 versus 4-4.49 m/s HR (95% CI) 1.36 (1.13–1.75) for Vmax 5-5.49 versus 4-4.49 m/s **HR (95% CI) 1.20 (1.01–1.37) for Vmax ≥5.5 m/s versus 4-4.49 m/s** 5-year survival of asymptomatic or minimally symptomatic patients was 85±5% for Vmax 4 to 4.49 m/s, 92±5% for Vmax 4.5 to 4.99 m/s, 81±7% for Vmax 5 to 5.49 m/s, and 75±7% for Vmax ≥5.5 m/s **All-cause mortality (analysis 2, single threshold)** **HR (95% CI) 1.98 (1.47–2.68) for Vmax ≥5.0 m/s versus <5.0 m/s** 5-year survival was 86±5% for Vmax <5 m/s and 73±4% for Vmax ≥5 m/s

Reference	Bohbot 2017[30]	
Comments and risk of bias	For analysis 1 and analysis 2:	
	1. Study participation	LOW
	2. Study attrition	LOW
	3. Prognostic factor measurement	LOW
	4. Outcome Measurement	HIGH
	5. Study confounding	LOW
	6. Statistical analysis	LOW
	7. Other risk of bias	NA
	OVERALL RISK OF BIAS	HIGH

1

Reference	Bohbot 2019[26]
Study type and analysis	Retrospective chart review of patients identified between 2000 and 2016 Multivariable Cox proportional hazards model.
Number of participants and characteristics	N=1678 LVEF ≥60% n = 1108 LVEF <60% n = 570 LVEF <55% n = 239 **Inclusion criteria:** Aged ≥18 years, diagnosed on echocardiography with severe AS (defined as AVA ≤1 cm^2 and/or AVA normalized to body surface area [BSA] ≤0.6 cm^2/m^2, and Vmax ≥4 m/s) LVEF ≥50%, and no or minimal symptoms (e.g., atypical chest pain and elderly patients with minimal dyspnoea not clearly related to AS) at diagnosis. **Exclusion criteria:** (1) individuals with more than mild aortic and mitral regurgitation; (2) patients with prosthetic valves, congenital heart disease (with the exception of bicuspid aortic valves), supravalvular or subvalvular AS, or dynamic left ventricular (LV) outflow tract obstruction, and (3) individuals who declined to participate in the study. Demographic details

<table>
<tr><th>Reference</th><th>Bohbot 2019[26]</th></tr>
<tr><td></td><td>
• Mean (SD) age:
LVEF ≥60%: 75.8 (10.3) years
LVEF 55-59%: 75.8 (10.7) years
LVEF <55%: 76.3 (10.3) years
• Sex (male):
LVEF ≥60%: 46.7%
LVEF 55-59%: 54.7%
LVEF <55%: 57.7%

• Single vs multiple valve disease: NA
• Co-morbid cardiac abnormalities:
<table>
<tr><th></th><th>Coronary artery disease</th><th>Prior atrial fibrillation</th></tr>
<tr><td>LVEF ≥60%:</td><td>44%</td><td>21.6%</td></tr>
<tr><td>LVEF 55-59%:</td><td>37.8%</td><td>22.7%</td></tr>
<tr><td>LVEF <55%:</td><td>44.8%</td><td>31%</td></tr>
</table>
920 patients were initially managed surgically (patients underwent surgery within 3 months after baseline echocardiography), including 639 with LVEF ≥60% (69%), 164 with LVEF between 55% and 59% (18%), and 117 with LVEF <55% (13%).

Population source: prospectively identified from electronic database of 2 French and 1 Belgian tertiary centres
</td></tr>
<tr><td>Prognostic variables</td><td>LVEF ≥60% (referent group)
LVEF <60% n = 570

LVEF ≥55% (referent group)
LVEF <55% n = 239</td></tr>
<tr><td>Confounders</td><td>The following covariates considered to have a potential prognostic impact (on the basis of epidemiological data) were included: age, sex, body surface area, hypertension, coronary artery disease, history of myocardial infarction, history of atrial fibrillation, comorbidity index, and aortic valve area.</td></tr>
<tr><td>Outcomes and effect sizes</td><td>All-cause mortality (analysis 1, multiple thresholds)
HR (95% CI) 1.25 (0.89–1.75) for LVEF 55-59% versus ≥60%</td></tr>
</table>

Reference	Bohbot 2019[26]
	HR (95% CI) 2.29 (1.68–3.17) for LVEF <55% versus ≥60% After further adjustment for surgery, treated as a time-dependent variable **HR (95% CI): 2.77 (2.13 to 3.61)** for LVEF <55% versus ≥60% **All-cause mortality (analysis 2, single threshold)** HR (95% CI) 2.18 (1.60–2.96) for LVEF <55% versus ≥55% After further adjustment for surgery, treated as a time-dependent variable **HR (95% CI): 2.18 (1.60 to 2.96)** for LVEF <55% versus ≥55% **All-cause mortality (analysis 3, stratified by operative status)** **Conservative management (n=758)** 249 deaths (33%) were recorded and 329 (43%) underwent surgery during follow-up. Five-year survival rate was 54 ± 3% for patients with LVEF ≥60%, 46 ± 6% for patients with LVEF between 55% and 59%, and 38 ± 7% for patients with LVEF <55% HR (95% CI) 1.16 (0.73–1.86) for LVEF 55-59% versus ≥60% HR (95% CI) 2.44 (1.51–3.94) for LVEF <55% versus ≥60% **HR (95% CI) 2.34 (1.49–3.67) for LVEF <55% versus ≥55%** **Surgical management (n=920)** 151 deaths (16%) were recorded during follow-up. Five-year survival rate was 83 ± 2% for patients with LVEF ≥60%, 81 ± 4% for patients with LVEF between 55% and 59%, and 68 ± 6% for patients with LVEF <55% HR (95% CI) 1.27 (0.76–2.12) for LVEF 55-59% versus ≥60% HR (95% CI) 2.51 (1.58–4.00) for LVEF <55% versus ≥60% **HR (95% CI) 2.38 (1.52–3.72) for LVEF <55% versus ≥55%** Overall 5-year survival rates (surgically or medically managed) were 72 ± 2% for patients with LVEF ≥60%, 74 ± 2% for patients with LVEF between 55% and 59%, and 59 ± 4% for patients with LVEF <55%

Reference	Bohbot 2019[26]	
	Analyses of intra-observer (R = 0.96; ICC = 0.95; CV = 3%), inter-observer (R = 0.90; ICC = 0.87, CV = 4.5%), and Inter-centre (R values between 0.88 and 0.90; ICC-values between 0.83 and 0.89, and CV values between 4.2% and 4.6%) for LVEF measurement showed good reproducibility. Pearson correlation coefficient (R) Intraclass correlation coefficient (ICC) Coefficient of variation (CV)	
Comments	1. Study participation 2. Study attrition 3. Prognostic factor measurement 4. Outcome Measurement 5. Study confounding 6. Statistical analysis 7. Other risk of bias OVERALL RISK OF BIAS	HIGH LOW LOW LOW LOW LOW NA HIGH

Reference	Campo 2019[39]
Study type and analysis	Retrospective chart review of patients identified between January 2005 and December 2013 Multivariable Cox proportional hazards model.
Number of participants and characteristics	N=265 (out of total of 4998 echocardiograms performed), but useable data only for those with surgery recommended at baseline (n=104) Number in each LVEF group unclear **Inclusion criteria:** severe aortic stenosis, defined as AVA ≤1 cm^2, and/or mean gradient ≥40 mmHg, and/or Vmax ≥4 m/s, and asymptomatic (absence of angina, dyspnoea or light-headedness/syncope attributable to AS. **Exclusion criteria:** inoperable (n=5), no recommendation for further follow-up or recommendation unknown (n=38) **In surgery group** • **Mean (SD) age**: 68.1 (11.7) years • **Sex**: 69% male

Reference	Campo 2019[39]

	• **Single vs multiple valve disease**: unclear
	• **Co-morbid cardiac abnormalities**:
	  ○ Chronic congestive heart failure: 6%
	  ○ Arrhythmia: 18%
	  ○ Coronary artery disease: 37%
	
	Population source: single tertiary care centre, probably from a consecutive sample

Prognostic variable	LVEF >50% LVEF ≤50% (referent)
Confounders	AVR, age, sex, mean gradient, EF, coronary artery disease
Outcomes and effect sizes	**All-cause mortality in the group with surgery recommended** HR 0.92 (95% CI 0.87 to 0.97) for EF>50% versus ≤50% [Note: HR inverted to match direction of effect as reported in other studies (where >1 = risk factor)] 3-year mortality 9% (9 events)
Comments	1. Study participation HIGH 2. Study attrition LOW 3. Prognostic factor measurement HIGH 4. Outcome Measurement LOW 5. Study confounding HIGH 6. Statistical analysis VERY HIGH 7. Other risk of bias NA OVERALL RISK OF BIAS VERY HIGH

1

Reference	Clavel 2014[56]
Study type and analysis	Prospective cohort study. Multivariable Cox proportional hazards analysis

Reference	Clavel 2014[56]

Number of participants and characteristics	N=1953 [565 in asymptomatic subgroup (defined as asymptomatic AS with normal ejection fraction and no previous myocardial infarction.]
	In the asymptomatic group:
	Activated BNP <2 times normal (n=130)
	Activated BNP 2 to 3 times normal (n=68)
	Activated BNP ≥3 times normal (n=144)
	Normal BNP level (n=222; referent)
	
	Inclusion criteria: consecutive patients who were diagnosed with moderate or severe AS based on aortic valve area (AVA) of ≤1.5 cm^2 by Doppler echocardiography and who underwent this combined clinical, hormonal, and Doppler echocardiographic assessment.
	
	Exclusion criteria: known rheumatic valve disease (clinically and/or echocardiographically); congenital heart disease (except overt or unknown bicuspid valve or patent foramen ovale); previous valvular surgery; acute myocardial infarction within 8 weeks preceding AS diagnosis; atrial fibrillation with rapid ventricular response; history or current endocarditis; pericarditis with or without tamponade; sepsis; severe liver, kidney, or brain disease except old stroke; hyperparathyroidism; or Cushing disease
	
	Venous blood samples were drawn from an antecubital vein. Plasma separation was immediately performed and plasma samples were frozen. Plasma BNP levels were determined by immunoenzymatic assay within 3 days. The ratio between measured serum BNP level and maximal normal BNP level for age and sex (BNP ratio) was calculated for each patient. The maximal normal values of BNP specific to age and sex were derived from Mayo Clinic laboratory procedures.
	Patients with elevated BNP levels (i.e., BNP ratio >1) were considered as displaying BNP clinical activation
	
	• **Mean (SD) age**: 74 (13) years
	• **Sex**: 55% male
	• **Single vs multiple valve disease**: not reported
	• **Co-morbid cardiac abnormalities**:
	  ○ Hypertension, 63%
	  ○ Atrial fibrillation, 11%
	  ○ Prior MI, 0%
	  ○ Prior open-heart surgery, 4%
	• **Mean (SD) left ventricular ejection fraction:** 57 (15)%

Reference	Clavel 2014[56]
	During a mean follow-up of 4.3 (2.4) years, there were 265 AVRs and 227 deaths and overall survival at 2, 5, and 8 years was 80±2%, 62±2%, and 54±3%. The survival of isolated AS 8 years after diagnosis was 75±4% without versus 38±4% with BNP clinical activation. **Population source:** Prospective assessment of consecutive patients Outcome data was from electronic records of events from internal computerised databases and from the Social Security Death Index.
Prognostic variable	Activated BNP (n=342) Activated BNP <2 times normal (n=130) Activated BNP 2 to 3 times normal (n=68) Activated BNP ≥3 times normal (n=144) Normal BNP level (n=222; referent)
Confounders	Age, sex, body surface area, atrial fibrillation, Charlson score index, symptoms, creatinine level, haemoglobin level, systolic blood pressure, indexed aortic valve area, indexed stroke volume, and LV ejection fraction. Further adjusted for aortic valve replacement as a time-dependent variable
Outcomes and effect sizes	**All-cause mortality** HR 2.35 (1.57–3.56) for activated versus normal BNP HR 2.10 (1.32–3.36) for activated BNP <2-times normal versus normal BNP HR 2.25 (1.31–3.87) for activated BNP 2-3-times normal versus normal BNP HR 3.93 (2.40–6.43) for activated BNP ≥3-times normal versus normal BNP **All-cause mortality in severe subgroup,** number unknown (mean gradient >40 mm Hg, peak aortic jet velocity >4m/s, or AVA <1.0 cm^2) HR 3.02 (1.31–6.93) for BNP ratio 1 to 2 versus BNP ratio ≤1 HR 4.64 (1.99–10.81) for BNP ratio 2 to 3 versus BNP ratio ≤1 HR 7.38 (3.27–16.66) for BNP ratio ≥3 versus BNP ratio ≤1
Comments	**For majority of outcomes** 1. Study participation HIGH 2. Study attrition HIGH 3. Prognostic factor measurement LOW 4. Outcome Measurement HIGH 5. Study confounding LOW 6. Statistical analysis HIGH 7. Other risk of bias LOW

Reference	Clavel 2014[56]	
	OVERALL RISK OF BIAS	VERY HIGH
	For moderate-to-severe, activated versus normal BNP	
	1. Study participation	HIGH
	2. Study attrition	HIGH
	3. Prognostic factor measurement	LOW
	4. Outcome Measurement	HIGH
	5. Study confounding	LOW
	6. Statistical analysis	LOW
	7. Other risk of bias	LOW
	OVERALL RISK OF BIAS	VERY HIGH

1

Reference	Henri 2016[107]
Study type and analysis	Prospective cohort study. Multivariable Cox proportional hazards analysis
Number of participants and characteristics	N=69 Median annualised change in BNP >20pg/ml/year n=34 Median annualised change in BNP ≤20pg/ml/year (referent) n=35 **Inclusion criteria:** asymptomatic patients (confirmed by exercise testing) with at least moderate AS (aortic valve area < 1.5 cm2) and preserved LVEF (>50%) referred for clinical evaluation and Doppler echocardiography to a single heart valve clinic **Exclusion criteria:** concomitant more than mild mitral valve disease or aortic regurgitation • **Mean (SD) age**: 70 (12) years • **Sex**: 42% male • **Single vs multiple valve disease**: multiple excluded • **Co-morbid cardiac abnormalities**: ○ Hypertension, 54%

Reference	Henri 2016[107]
	○ Atrial fibrillation, 9% ○ Coronary artery disease, 20% • **Baseline BNP, pg/ml (median**) 96±135 **Population source**: consecutive sample from a single centre Aortic valve replacement was performed in 37 (54%) patients motivated by the occurrence of symptoms in 27 (39%) patients and by an abnormal exercise test showing symptoms clearly related to AS in 10 (14%) patients. Among the 6 (9%) remaining events, 4 (6%) were related to the development of patient symptoms but were treated medically because of prohibitive high surgical risk and 2 (3%) patients died from a cardiovascular cause. Follow-up information was obtained after a complete medical chart review and discussions with the patients and/or general physicians. The follow-up was complete in 66 patients (96%). Duration of follow-up between the baseline and the last measurement was 24±17 months. Duration of follow-up between baseline BNP measurement and last follow-up was 30±19 months
Prognostic variable	Median annualised change in BNP >20pg/ml/year Median annualised change in BNP ≤20pg/ml/year (referent) BNP level measurement was performed at baseline and repeated after at least 6 months of follow-up, and then, after every 6 or 12 months. Venous blood samples were drawn at rest. Annualised BNP changes were calculated as the BNP changes (difference between the last BNP measurement obtained during the follow-up and the baseline BNP measurement at inclusion) divided by the time between baseline measurement and last follow-up measurement
Confounders	Gender and baseline BNP levels were forced into the first multivariable model regardless of the P value as they may influence annualized BNP changes. Variables with a P value < 0.10 in univariable were incorporated into the second multivariable model. **Included in the model:** age, dyslipidaemia and echocardiographic variables (peak aortic velocity and indexed left atrial area)
Outcomes and effect sizes	**Adverse cardiac events** (symptoms, aortic valve replacement as indicated by symptoms or LV dysfunction according current class I indication, or cardiovascular death) HR (95% CI) 2.73 (1.27 to 5.86) for >20pg/ml/year versus ≤20pg/ml/year 43 patients (62%) presented a cardiac event.

Reference	Henri 2016[107]	
Comments	1. Study participation	LOW
	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
	Indirect outcome and population	

1

Reference	Kanamori 2019[121]
Study type and analysis	Retrospective cohort study Multivariable Cox proportional hazards model.
Number of participants and characteristics	N=1309 1. AVA >0.80 cm^2, N=645 2. 0.8 cm^2 ≥AVA>0.6 cm^2, N=465 3. AVA ≤0.6 cm^2, N=199 **Inclusion criteria:** asymptomatic severe AS managed conservatively after echo (severe: Vmax >4.0 m/s, MPG >40 mm Hg, or AVA <1.0 cm^2; asymptomatic: absence of AS symptoms: angina, syncope, and heart failure symptoms including dyspnoea) diagnosed for the first time during the study period, and LVEF ≥50%. **Exclusion criteria:** AVR selected as the initial treatment strategy after the index echocardiography (n=1197), symptomatic AS (n=1100), LVEF <50% (n=123), symptomatic status not available (n=1), LVEF unknown (n=5), and AVA unknown (n=80)

	AVA >0.80	**0.8 cm^2 ≥AVA>0.6 cm^2**	**AVA ≤0.6 cm^2**
• **Mean (SD) age (years)**:	76 (9)	78 (9),	81 (9)
• **Sex, male (%)**:	45.9	32.6	28.1

Reference	Kanamori 2019[121]			
	• **Comorbid moderate or severe HVD)**	33.8	27.5	31.2
	• **Co-morbid cardiac abnormalities (%)**:			
	○ Prior percutaneous coronary intervention	17.4	16.1	11.6
	○ Prior CABG	4.8	5.4	4.0
	○ Prior open heart surgery	8.1	10.8	8.5
	○ AF or flutter	17.8	19.6	22.6
	○ Coronary artery disease	27.1	24.9	23.1
	○ EuroSCORE II	2.1	2.7	2.9
	○ STS score	3.0	3.7	4.1
	Aetiology of AS			
	○ Degenerative	88.8	89.0	91.0
	○ Congenital	6.7	5.6	4.5
	○ Rheumatic	3.7	4.9	2.5
	Population source: consecutive patients with severe AS enrolled in the CURRENT AS registry of 27 centres in Japan between January 2003 and December 2011			
Prognostic variable	AVA >0.80 cm^2 (referent) 0.8 cm^2 ≥AVA>0.6 cm^2 AVA ≤0.6 cm^2 AVA calculated using the standard continuity equation			
Confounders	Age, sex, body mass index, hypertension, current smoking, diabetes mellitus on insulin, coronary artery disease, prior myocardial infarction, prior symptomatic stroke, atrial fibrillation or flutter, aorta/peripheral artery disease, serum creatinine, haemodialysis, anaemia, liver cirrhosis, malignancy currently under treatment, chronic lung disease, any valvular disease, LVEF ≥68% and TR pressure gradient ≥40 mm Hg			
Outcomes and effect sizes	**Composite of aortic valve-related death or hospitalization due to HF (number of events in groups 1, 2 and 3: 124, 106, 67)** HR 1.34 (1.01–1.78) for 0.8 ≥AVA>0.6 versus AVA >0.80 cm^2 HR 2.21 (1.56–3.11) for AVA≤0.6 versus AVA >0.80 cm^2 **All-cause mortality (cumulative 5- year incidence: number of events in groups 1, 2 and 3: 160, 160, 94)** HR 1.49 (1.17–1.89) for 0.8 ≥AVA>0.6 versus AVA >0.80 cm^2 HR 2.61 (1.96–3.47) for AVA≤0.6 versus AVA >0.80 cm^2			

Reference	Kanamori 2019[121]
	Cardiovascular mortality (cumulative 5- year incidence: number of events in groups 1, 2 and 3: 91, 85, 66) HR 1.48 (1.07–2.05) for 0.8 ≥AVA>0.6 versus AVA >0.80 cm^2 HR 3.36 (2.34–4.83) for AVA0.6 versus AVA >0.80 cm^2 **Aortic valve-related mortality (cumulative 5- year incidence: number of events in groups 1, 2 and 3: 46, 56, 42)** HR 2.01 (1.31–3.08) for 0.8 ≥AVA>0.6 versus AVA >0.80 cm^2 HR 4.53 (2.79–7.34) for AVA≤0.6 versus AVA >0.80 cm^2 **Heart failure hospitalisation (cumulative 5- year incidence: number of events in groups 1, 2 and 3: 97, 83, 50)** HR 1.33 (0.96–1.83) for 0.8 ≥AVA>0.6 versus AVA >0.80 cm^2 HR 1.95 (1.31–2.92) for AVA≤0.6 versus AVA >0.80 cm^2
Comments	**Composite of aortic valve-related death or hospitalization due to HF** 1. Study participation LOW 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement HIGH 5. Study confounding LOW 6. Statistical analysis LOW 7. Other risk of bias NA OVERALL RISK OF BIAS HIGH **All-cause mortality** 1. Study participation LOW 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement HIGH 5. Study confounding LOW 6. Statistical analysis LOW 7. Other risk of bias NA

Reference	Kanamori 2019[121]	
	OVERALL RISK OF BIAS	HIGH
	Cardiovascular mortality	
	1. Study participation	LOW
	2. Study attrition	LOW
	3. Prognostic factor measurement	LOW
	4. Outcome Measurement	HIGH
	5. Study confounding	LOW
	6. Statistical analysis	LOW
	7. Other risk of bias	NA
	OVERALL RISK OF BIAS	HIGH
	Aortic valve-related mortality	
	1. Study participation	LOW
	2. Study attrition	LOW
	3. Prognostic factor measurement	LOW
	4. Outcome Measurement	HIGH
	5. Study confounding	LOW
	6. Statistical analysis	HIGH
	7. Other risk of bias	NA
	OVERALL RISK OF BIAS	VERY HIGH
	Heart failure hospitalisation	
	1. Study participation	LOW
	2. Study attrition	LOW
	3. Prognostic factor measurement	LOW
	4. Outcome Measurement	HIGH
	5. Study confounding	LOW
	6. Statistical analysis	HIGH
	7. Other risk of bias	NA

Reference	Kanamori 2019[121]
	OVERALL RISK OF BIAS VERY HIGH Most of this study period was before transcatheter aortic valve implantation introduction in Japan.

Reference	Kang 2010[125]
Study type and analysis	Prospective registry from 1996-2006 including all consecutive patients with AS undergoing echocardiography. Cox proportional hazard model adjusted for European System for Cardiac Operative Risk Evaluation (EuroSCORE).
Number of participants and characteristics	N=95 AV velocity <5 m/s, n=63 AV velocity ≥5 m/s, n=32 **Inclusion criteria:** Asymptomatic patients with very severe AS who were potential candidates for early surgery. Very severe AS was defined as a critical stenosis in the AV area ≤0.75 cm2 fulfilling one of the following criteria: a peak aortic velocity ≥4.5 m/s or a mean transaortic pressure gradient ≥50 mm Hg on Doppler echocardiography. **Exclusion criteria:** Exertional dyspnoea, syncope, presyncope or angina, left ventricular (LV) ejection fraction (EF)<50%, moderate or severe aortic regurgitation, or significant mitral valve disease and those who were not candidates for early surgery because of age >85 years or the presence of coexisting malignancies, history of coronary artery disease or regional wall motion abnormalities Our subgroup excludes those undergoing early surgery • **Mean (SD) age**: 63 (12) years • **Sex**: 46% male • **Valve surgery**: 46/95 had surgery during follow-up • **Single vs multiple valve disease**: unclear

Reference	Kang 2010[125]
	• **Co-morbid cardiac abnormalities**: o Atrial fibrillation: 8% • **Cause of AS** o Degenerative: 47% o Bicuspid: 41% o Rheumatic: 12% Population source: consecutive sample from multiple sites.
Prognostic variable	AV velocity ≥5 m/s versus the referent of <5m/s
Confounders	EuroSCORE, unclear if other variables included
Outcomes and effect sizes	**Cardiac mortality** HR 1.59 (1.22–2.06) for AV velocity ≥5 m/s versus <5m/s Overall: 18 cardiac deaths In those remaining asymptomatic: 7 sudden deaths, 6 non cardiac deaths In those developing symptoms: 1 death from endocarditis after surgery and 4 non-cardiac deaths after surgery; in those without surgery 2 sudden deaths, 7 congestive heart failure deaths and 1 death from endocarditis.
Comments and risk of bias	1. Study participation — UNCLEAR 2. Study attrition — LOW 3. Prognostic factor measurement — LOW 4. Outcome Measurement — HIGH 5. Study confounding — LOW 6. Statistical analysis — HIGH 7. Other risk of bias — NA OVERALL RISK OF BIAS — VERY HIGH

Reference	Kitai 2017[131]
Study type and analysis	CURRENT AS registry: retrospective multicentre registry enrolling patients across 27 centres in Japan between January 2003 and December 2011. Multivariable Cox proportional hazards model
Number of participants and characteristics	N=1517 [5 missing data required for classification not included in the analysis] Patients were divided into groups according to the 2014 ACC/AHA guideline recommendations for surgery as follows. Group 1 (N=122) met the recommendation for surgery: • high-gradient (HG)-AS (Vmax>=4.0m/s or mPG>=40mmHg) with ejection fraction (EF)<50%, *or* • very HG-AS (Vmax>=5.0m/s or mPG>=60mmHg) Group 2 (N=1390) did not meet the recommendation for surgery, and was further subdivided into • HG-AS with preserved EF (HGpEF-AS, N=498) • low-gradient (LG)-AS, but AVA<1.0cm^2 (N=892). **Inclusion criteria:** consecutive patients in the hospital database for transthoracic echocardiography meeting criteria for severe aortic stenosis [peak aortic jet velocity (Vmax) >4.0 m/s, mean aortic pressure gradient >40 mmHg or aortic valve area <1.0 cm^2] for the first time during the study period, who had no AS-related symptoms and were managed conservatively under watchful waiting at the time of diagnosis. **Exclusion criteria:** Initially symptomatic, or initially asymptomatic but with plan for aortic valve intervention **Group 1** / **Group 2** • **Mean (SD) age (years)**: 78 (11) / 78 (9) • **Sex, male (%)**: 32.0 / 40.5 • **Surgical AVR or TAVI (cumulative 5-year incidence, %)** 40.9 / 40.7 • **Comorbid moderate or severe HVD** 36 / 31 • **Co-morbid cardiac abnormalities (%)**:

Reference	Kitai 2017[131]		
	○ Prior percutaneous coronary intervention	10	18
	○ Prior CABG	3	6
	○ Prior open heart surgery	7	10
	○ AF or flutter	11	20
	○ Coronary artery disease	20	29
	○ EuroSCORE II	2.8	2.6
	○ STS score	3.5	3.5
	Aetiology of AS		
	○ Degenerative	87	90
	○ Congenital	7	5
	○ Rheumatic	4	4
	Population source: consecutive patients with severe AS enrolled in the CURRENT AS registry of 27 centres in Japan between January 2003 and December 2011 Median follow-up duration 1360 (IQR: 1069-16669) days		
Prognostic variables	**Analysis 1** Group 1 (N=122) met the recommendation for surgery (high-gradient (HG)-AS (Vmax>=4.0m/s or mPG>=40mmHg) with ejection fraction (EF)<50%, or very HG-AS (Vmax>=5.0m/s or mPG>=60mmHg)) Group 2, referent (N=1390) did not meet the recommendation for surgery **Analysis 2 (within group 2)** HG-AS with preserved EF (HGpEF-AS, N=498) Low-gradient (LG)-AS, but AVA<1.0cm^2 (N=892; referent). **Analysis 3 (within group 2)** Low-gradient (LG)-AS, with reduced EF <50% (N=103). Low-gradient (LG)-AS, with preserved EF ≥50% (N=789; referent).		
Confounders	All 19 considered in study were entered into multivariable analysis: age, male, BMI <22 kg/m^2, acute heart failure, hypertension, current smoking, diabetes mellitus on insulin therapy, coronary artery disease, past myocardial infarction, past symptomatic stroke, atrial fibrillation or flutter, aortic/peripheral vascular disease, haemodialysis, anaemia, liver cirrhosis, malignancy currently under treatment, chronic lung disease, any combined valvular disease and tricuspid regurgitation pressure gradient ≥40 mm Hg.		

Reference	Kitai 2017[131]
Outcomes and effect sizes	**Analysis 1** **Composite of aortic valve-related death or hospitalization due to HF (number of events in groups 1 and 2: 47/122, 319/1390)** HR 1.92 (1.37–2.68) for group 1 versus group 2 **All-cause mortality (cumulative 5- year incidence: number of events in groups 1 and 2: 57/122, 483/1390)** HR 1.45 (1.08–1.95) for group 1 versus group 2 **Cardiovascular mortality (cumulative 5- year incidence: number of events in groups 1 and 2: 39/122, 282/1390)** HR 1.84(1.28–2.64) for group 1 versus group 2 **Aortic valve-related mortality (cumulative 5- year incidence: number of events in groups 1 and 2: 29/122, 166/1390)** HR 2.34 (1.52–3.60) for group 1 versus group 2 **Heart failure hospitalisation (cumulative 5- year incidence: number of events in groups 1 and 2: 37/122, 245/1390)** HR 1.96 (1.34–2.87) for group 1 versus group 2 **Analysis 2** **Composite of aortic valve-related death or hospitalization due to HF (cumulative 5- year incidence: number of events in HGpEF-AS and LG-AS: 124/498, 195/892)** HR 1.45 (1.11–1.89) for HGpEF-AS versus LG-AS **All-cause mortality (cumulative 5- year incidence: number of events in HGpEF-AS and LG-AS: 178/498, 305/892)** HR 1.42 (1.14–1.76) for HGpEF-AS versus LG-AS **Cardiovascular mortality (cumulative 5- year incidence: number of events in HGpEF-AS and LG-AS: 11498, 172/892)** HR 1.56 (1.18–2.07) for HGpEF-AS versus LG-AS **Aortic valve-related mortality (cumulative 5- year incidence: number of events in HGpEF-AS and LG-AS: 71/498, 95/892)** HR 1.77 (1.23–2.55) for HGpEF-AS versus LG-AS

Reference	Kitai 2017[131]
	Heart failure hospitalisation (cumulative 5- year incidence: number of events in HGpEF-AS and LG-AS: 92/498, 153/892) HR 1.28 (0.94–1.74) for HGpEF-AS versus LG-AS **Analysis 3** **Composite of aortic valve-related death or hospitalization due to HF (cumulative 5- year incidence: number of events in LGrEF-AS and LGpEF-AS: 41/103, 154/789)** HR 2.55 (1.68–3.86) for LGrEF-AS versus LGpEF-AS **All-cause mortality (cumulative 5- year incidence: number of events in LGrEF-AS and LGpEF-AS: 76/103, 229/789)** HR 2.74 (1.99–3.78) for LGrEF-AS versus LGpEF-AS **Cardiovascular mortality (cumulative 5- year incidence: number of events in LGrEF-AS and LGpEF-AS: 53/103, 119/789)** HR 3.23 (2.13–4.87) for LGrEF-AS versus LGpEF-AS **Aortic valve-related mortality (cumulative 5- year incidence: number of events in LGrEF-AS and LGpEF-AS: 3103, 65/789)** HR 4.06 (2.31–7.13) for LGrEF-AS versus LGpEF-AS **Heart failure hospitalisation (cumulative 5- year incidence: number of events in LGrEF-AS and LGpEF-AS: 3103, 123/789)** HR 2.37 (1.46–3.87) for LGrEF-AS versus LGpEF-AS
Comments	**For most comparisons and outcomes (exceptions noted below):** 1. Study participation LOW 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement HIGH 5. Study confounding LOW 6. Statistical analysis LOW 7. Other risk of bias LOW

Reference	Kitai 2017[131]	
	OVERALL RISK OF BIAS	HIGH
	For analysis 2, AV-related mortality and analysis 3 cardiovascular mortality, AV-related mortality and HF hospitalisation outcomes:	
	1. Study participation	LOW
	2. Study attrition	LOW
	3. Prognostic factor measurement	LOW
	4. Outcome Measurement	HIGH
	5. Study confounding	LOW
	6. Statistical analysis	HIGH
	7. Other risk of bias	LOW
	OVERALL RISK OF BIAS	VERY HIGH

1

Reference	Lancellotti 2018[140]
Study type and analysis	Retrospective cohort study based on the HAVEC registry, which was assembled by merging data from prospectively gathered institutional databases from 10 heart valve clinics in Europe, Canada, and the USA. Data were collected from January 2001 to December 2014. Multivariable Cox proportional hazards model.
Number of participants and characteristics	Total n = 1375, 834 with severe aortic stenosis In the severe group: Aortic jet velocity ≥5 m/s: n = 103 LVEF <60%: n = 267 **Inclusion criteria:** Asymptomatic aortic stenosis (AS) with an aortic valve area of 1.5 cm^2 or less and preserved left ventricular ejection fraction (LVEF) > 50% at entry. AS diagnosed with the use of 2-dimension echocardiography at 1 of the participating centres and followed-up according to available guidelines on a regular basis at heart valve clinics. **Exclusion criteria:**

Reference	Lancellotti 2018[140]
	Aortic valve area (AVA) >1.5 cm^2; class I indications for AVR (rest AS–related or exercise AS–related symptoms [i.e., angina, syncope, and dyspnoea] or LV ejection fraction [EF] < 50%); concomitant congenital heart valve disease more than mild mitral, tricuspid, or pulmonic valve disease; or prior valve surgery Note: subgroup analysis available for severe AS • **Mean (SD) age**: 72 (12) years • **Sex**: 57.7% male • **Valve surgery**: 388/861 with severe AS had aortic valve replacement (AVR) during follow-up (patient censored at time of AVR) • **Single vs multiple valve disease**: unclear • **Co-morbid cardiac abnormalities**: ○ Mean (SD) systolic BP: 140 (20) **Population source:** registry data from multiple sites, based on consecutive patients. 388 (22%) excluded based on missing data on LVEF or AS severity.
Prognostic variables	Aortic jet velocity ≥5 m/s (referent <5 m/s) LVEF <60%: n = 267 (referent ≥60%)
Confounders	Covariates selected on the basis of their known link to outcome in patients with AS: age, sex, comorbidities, AS severity, and LVEF
Outcomes and effect sizes	<u>Severe AS with AVR censoring (n=861):</u> **All-cause mortality** HR (95% CI) 2.05 (1.01-4.16) for peak aortic velocity ≥5 m/s versus <5 m/s HR (95% CI) 5.01 (2.93-8.57) for LVEF <60% versus ≥60% **Cardiovascular mortality** HR (95% CI) 6.31 (2.51-15.9) for peak aortic velocity ≥5 m/s versus <5 m/s HR (95% CI) 4.47 (2.06-9.70) for LVEF <60% versus ≥60% **Note:** 2-year, 4-year, and 8-year overall survival rates were 92%, 80%, and 65%, respectively 2-year, 4-year, and 8-year cardiovascular death–free survival rates were 96%, 87%, and 71%, respectively <u>Severe AS post-AVR outcomes (n=388)</u>

Reference	Lancellotti 2018[140]	
	Post-operative survival HR (95% CI) 2.20 (1.16-4.18) for peak aortic velocity ≥5 m/s versus <5 m/s LVEF <60% versus ≥60% was not associated with reduced postoperative survival in multivariable analysis.	
Comments and 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	NA
	OVERALL RISK OF BIAS	VERY HIGH

Reference	**Magne 2019[158]** *Included studies: Lancellotti 2010, Zito 2011, Dahl 2012, Kearney 2012, Yingchoncharoen 2012, Kusunose 2014, Sato et al 2014, Carstensen 2015, Nagata 2015, Salaun 2017*
Study type and analysis	Individual participant data (IPD) meta-analysis of 10 studies Multivariable Cox proportional hazard model
Number of participants and characteristics	N=1067 LV-GLS >14.7 n=722 LV-GLS ≤14.7 n=345 In subgroup with LVEF ≥60% LV-GLS >14.7 n=513 LV-GLS ≤14.7 n=221 **Inclusion criteria:** Studies were selected for the meta-analysis if they included patients with all of the following criteria: 1) asymptomatic; 2) preserved LVEF (i.e., >50%); 3) greater than or equal to moderate AS, as defined by current guidelines at the time of the study; 4) quantification of the LVGLS using 2-dimensional speckle tracking; and 5) availability of outcome of interest for the current analysis (i.e., all-cause death). **Exclusion criteria:**

Reference	**Magne 2019**[158] *Included studies: Lancellotti 2010, Zito 2011, Dahl 2012, Kearney 2012, Yingchoncharoen 2012, Kusunose 2014, Sato et al 2014, Carstensen 2015, Nagata 2015, Salaun 2017*
	Only post-operative data available • **Mean (SD) age**: 74 (10) years • **Sex**: 56% male • **Valve surgery**: not stated • **Single vs multiple valve disease**: unclear • Severe AS: 82% • **Co-morbid cardiac abnormalities**: ○ Coronary artery disease: 26% Population source: individual participant data gained from study authors of 10 original studies of unique patient cohorts
Prognostic variable	LV-GLS ≤14.7 versus >14.7 (referent) *Threshold determined by AUC analysis of the included data*
Confounders	Age, gender, AVAi, and LVEF
Outcomes and effect sizes	**Mortality** HR **2.62 (1.66-4.13)** for LV-GLS ≤14.7 versus >14.7 HR **2.69 (1.53-4.74)** for LV-GLS ≤14.7 versus >14.7 in subgroup with LVEF ≥60%
Comments	RISK: HIGH Rationale for risk: unclear if all relevant studies have been identified and biases in primary studies not assessed or accounted for

Reference	**Marechaux 2016**[166]
Study type and analysis	Prospective database registry with retrospective follow-up. Patients identified and included in the database between 2000 and 2012 at the echocardiography laboratories of two tertiary centres in France. Multivariable Cox proportional hazard model.

Reference	Marechaux 2016[166]

Number of participants and characteristics	N=199
	
	<u>Analysis 1:</u>
	AVA ≤0.6 cm^2, n=39
	AVA 0.6-0.8 cm^2, n=80
	AVA 0.8-1.0 cm^2, n=80
	
	<u>Analysis 2:</u>
	AVA ≤0.6 cm^2, n=39
	AVA >0.6 cm^2, n=160
	
	Inclusion criteria:
	Patients aged >18 years diagnosed with severe aortic stenosis (aortic valve area ≤1.0 cm^2) and left ventricular ejection fraction ≥50%.
	
	Exclusion criteria:
	Patients with any of the following: more than mild aortic and/or mitral regurgitation; prosthetic heart valves, congenital heart disease (with the exception of bicuspid aortic valves); supravalvular or subvalvular aortic stenosis; dynamic left ventricular outflow tract obstruction; symptoms by history or on exercise testing, including angina, syncope or dyspnoea. Those who denied authorisation for research participation were also excluded.
	
	• **Mean (SD) age**: 69 (14) years
	• **Sex**: 55% male
	• **Valve surgery**: 112/199 had aortic valve replacement during follow-up
	• **Single vs multiple valve disease**: Unclear – those with more than mild aortic and/or mitral regurgitation were excluded.
	• **Co-morbid cardiac abnormalities**:
	  ○ Coronary artery disease: 38%
	  ○ History of atrial fibrillation: 23%
	  ○ Hypertension: 59%
	  ○ Median (IQR) Charlson comorbidity index: 1 (1-2)
	• Median (IQR) left ventricular ejection fraction: 65 (58-71)%

Reference	Marechaux 2016[166]
	Population source: Those matching inclusion criteria between 2000 and 2012 at two sites. Unclear if consecutive patients considered.
Prognostic variable	**In those treated initially with medical management strategy:** Analysis 1: AVA ≤60 cm^2 AVA 0.6-0.8 cm^2 AVA 0.8-1.0 cm^2 (referent) Analysis 2: AVA ≤60 cm^2 AVA >60 cm^2 (referent) Estimated median follow-up, 48 months
Confounders	Age, sex, hypertension, coronary artery disease, history of atrial fibrillation, Charlson comorbidity index and left ventricular ejection fraction Note: for the all-cause mortality outcome only, data was also adjusted for aortic valve replacement in a separate analysis Have not adjusted for all confounders listed in protocol, but factors adjusted for include some of the components of risk scores pre-specified. No adjustment for any frailty measures. Model-building techniques were not used and covariates with potential prognostic impact on an epidemiological basis were selected.
Outcomes and effect sizes	**All-cause mortality during follow-up** • HR 2.52 (95% CI 1.20-5.29) for AVA ≤0.6 cm^2 vs. >0.6 cm^2 • **HR 3.39 (95% CI 1.80-6.40) for AVA ≤0.6 cm^2 vs. >0.6 cm^2 (further adjustment for aortic valve replacement as time-dependent variable)** Note: cumulative overall mortality at 12, 24 and 48 months was as follows: • 17±6%, 20±7%and 36±9%, respectively, in the AVA ≤0.6 cm^2 group

Reference	Marechaux 2016[166]
	• 5±2%, 12±3%and 19±4%, respectively, in the AVA >0.6 cm^2 group **All-cause mortality or aortic valve replacement surgery during follow-up** • **HR 2.22 (95% CI 1.41 to 3.52) for AVA ≤0.6 cm^2 vs. AVA 0.8-1.0 cm^2** • HR 1.38 (95% CI 0.93-2.05) for AVA 0.6-0.8 cm^2 vs. AVA 0.8-1.0 cm^2 Note: Estimated median follow-up was 48 months. N=137 patients reached an end-point during follow-up (112 underwent aortic valve replacement and 36 died). Of 25 patients that died without aortic valve replacement, 5 patients (20%) were within the AVA ≤0.6 cm^2 group, 8 patients (32%) were within the AVA 0.6-0.8 cm^2 group and 12 patients were within the AVA 0.8-1.0 cm^2 group. Event-free survival (from all-cause mortality or aortic valve replacement) at 12, 24 and 48 months was as follows: • 33±8, 20±7 and 11±5 months, respectively, for the AVA ≤0.6 cm^2 group • 49±6, 36±6 and 26±6 months, respectively, for the AVA 0.6-0.8 cm^2 group • 63±6, 51±6 and 34±6 months, respectively, for the AVA 0.8-1.0 cm^2 group
Comments and risk of bias	**All-cause mortality** 1. Study participation HIGH 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement HIGH 5. Study confounding LOW 6. Statistical analysis HIGH 7. Other risk of bias NA OVERALL RISK OF BIAS VERY HIGH **All-cause mortality or aortic valve replacement surgery** 1. Study participation HIGH 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement HIGH

Reference	Marechaux 2016[166]	
	5. Study confounding	LOW
	6. Statistical analysis	LOW
	7. Other risk of bias	NA
	OVERALL RISK OF BIAS	VERY HIGH
	Potential indirectness for outcome: composite of all-cause mortality and aortic valve replacement surgery	

1

Reference	Minamino-Muta 2020[179]
Study type and analysis	CURRENT AS registry: retrospective multicentre registry enrolling patients across 27 centres in Japan between January 2003 and December 2011. Multivariable logistic regression model
Number of participants and characteristics	N=1274, randomly divided into derivation (n=849) and validation (n=425) sets in a 2:1 fashion. <u>Prognostic analysis performed within the derivation set (n=849):</u> LVEF <60%, n=168 LVEF ≥60%, n=648 **Inclusion criteria:** consecutive patients in the hospital database for transthoracic echocardiography meeting criteria for severe aortic stenosis [peak aortic jet velocity (Vmax) >4.0 m/s, mean aortic pressure gradient >40 mmHg or aortic valve area <1.0 cm^2] for the first time during the study period, who had no AS-related symptoms and were managed conservatively under watchful waiting at the time of diagnosis. **Exclusion criteria:** history of percutaneous balloon valvuloplasty or surgical aortic valve repair/replacement/plasty; AS-related symptoms. • **Mean (SD) age**: 77.6 (9.3) years • **Sex**: 40% male • **Valve surgery**: Not reported • **Single vs multiple valve disease**: Any combined valvular disease (moderate or severe), 32% • **Co-morbid cardiac abnormalities**:

Reference	Minamino-Muta 2020[179]
	○ Hypertension, 72% ○ Coronary artery disease, 28% ○ Atrial fibrillation or flutter, 19% ○ Aortic/peripheral vascular disease, 8% • **Median (IQR) logistic EuroSCORE**: 8.5 (5.4-14.4)% • **Median (IQR) EuroSCORE II**: 2.6 (1.5-3.7)% • **Median (IQR) STS score (PROM)**: 3.4 (2.1-5.2)% • **Aetiology of aortic stenosis**: ○ Degenerative, 91% ○ Congenital (unicuspid, bicuspid or quadricuspid), 6% ○ Rheumatic, 4% ○ Infective endocarditis, 0.1% • **Mean (SD) left ventricular ejection fraction:** 66 (11)% Note: some of the above details obtained from supplementary tables associated with the study. Population source: Consecutive patients matching inclusion criteria from retrospective registry across 27 centres in Japan between January 2003 and December 2011. A total of 1517 patients in the registry matched inclusion criteria but some were excluded from the study sample due to death from causes other than AS-related death (n=118), receiving aortic valve replacement before occurrence of the primary outcome measure within 1 year (n=69) or lost to follow-up within 1 year (n=56).
Prognostic variable	**In those treated conservatively with watchful waiting:** LVEF <60% LVEF ≥60% (referent) Prognostic ability at 1 year follow-up assessed.
Confounders	Other prognostic variables included in the final multivariable analysis (those with 0.05 significance level on univariate analysis): diabetes mellitus, haemoglobin ≤11.0 g/dL, haemodialysis, chronic lung disease and any concomitant valve disease (moderate or severe). Note that only those variables that reached <0.10 significance level on univariate analysis were considered for entry into the multivariate analysis, which included: age, BMI <22, diabetes mellitus, coronary artery disease, aortic/peripheral vascular disease, haemodialysis, haemoglobin ≤11.0 g/dL, chronic lung disease, Vmax ≥4.5 m/s, LVEF<60%, high left ventricular mass index, and any

Reference	Minamino-Muta 2020[179]
	concomitant valve disease (moderate or severe). Subsequently, in the final model only those with <0.05 significance on univariate analysis were included, as detailed above. Have not adjusted for all confounders listed in protocol, but factors adjusted for include some of the components of risk scores pre-specified. No adjustment for any frailty measures.
Outcomes and effect sizes	**AS-related death or heart failure hospitalisation at 1 year** **OR 3.94 (95% CI 2.00 to 7.78) for LVEF <60% vs. LVEF ≥60%** Within 1 year after index echocardiography, 59 patients within derivation set developed AS-related events: 26 patients with heart failure hospitalisation and 33 patients with AS-related death. Breakdown of events for each prognostic group not reported.
Comments	1. Study participation LOW 2. Study attrition HIGH 3. Prognostic factor measurement LOW 4. Outcome Measurement HIGH 5. Study confounding LOW 6. Statistical analysis HIGH 7. Other risk of bias HIGH OVERALL RISK OF BIAS VERY HIGH Potential indirectness for outcome: composite outcome of aortic stenosis-related death or heart failure hospitalisation

1

Reference	Nakatsuma 2017[188]
Study type and analysis	CURRENT AS registry: retrospective multicentre registry enrolling patients across 27 centres in Japan between January 2003 and December 2011. Multivariable Cox proportional hazard model
Number of participants	N=596 in the asymptomatic subgroup (n=1075 in total study population) 4.0 m/s ≤ Vmax <4.5 m/s, n=364

Reference	Nakatsuma 2017[188]
and characteristics	4.5 ≤ Vmax <5.0 m/s, n=140 Vmax ≥5.0 m/s, n=92 **Inclusion criteria:** Those meeting criteria for severe aortic stenosis [peak aortic jet velocity (Vmax) >4.0 m/s, mean aortic pressure gradient >40 mmHg or aortic valve area <1.0 cm^2] for the first time during the study period who were managed conservatively under watchful waiting at the time of diagnosis - severe AS with Vmax ≥4.0 m/s and left ventricular ejection fraction ≥50% who were managed conservatively following index echocardiography. Note: the study includes those with both symptomatic and asymptomatic severe AS and provides data for each of these two groups separately. Only the asymptomatic group was included in this review as per the protocol. **Exclusion criteria:** Aortic valve replacement chosen as initial treatment strategy following index echocardiography; Vmax values unknown; Vmax values <4.0 m/s; left ventricular ejection fraction <50%. Note: all below information is for the asymptomatic subgroup • **Mean (SD) age**: 4.0 m/s ≤ Vmax <4.5 m/s, 77.2 (0.5) years; 4.5 ≤ Vmax <5.0 m/s, 76.4 (0.8) years; and Vmax ≥5.0 m/s, 77.6 (1.0) years • **Sex**: 4.0 m/s ≤ Vmax <4.5 m/s, 42%; 4.5 ≤ Vmax <5.0 m/s, 44%; and Vmax ≥5.0 m/s, 28% • **Valve surgery**: not reported • **Single vs multiple valve disease**: any combine valvular disease (moderate or severe) - 4.0 m/s ≤ Vmax <4.5 m/s, 30%; 4.5 ≤ Vmax <5.0 m/s, 34%; and Vmax ≥5.0 m/s, 36% • **Co-morbid cardiac abnormalities**: o Hypertension: 4.0 m/s ≤ Vmax <4.5 m/s, 69%; 4.5 ≤ Vmax <5.0 m/s, 64%; and Vmax ≥5.0 m/s, 59% o Coronary artery disease, 4.0 m/s ≤ Vmax <4.5 m/s, 20%; 4.5 ≤ Vmax <5.0 m/s, 19%; and Vmax ≥5.0 m/s, 14% o Atrial fibrillation or flutter, 4.0 m/s ≤ Vmax <4.5 m/s, 18%; 4.5 ≤ Vmax <5.0 m/s, 14%; and Vmax ≥5.0 m/s, 7.6% o Aortic/peripheral vascular disease, 4.0 m/s ≤ Vmax <4.5 m/s, 6.3%; 4.5 ≤ Vmax <5.0 m/s, 6.4%; and Vmax ≥5.0 m/s, 5.4% • **Past open heart surgery**: 4.0 m/s ≤ Vmax <4.5 m/s, 5%; 4.5 ≤ Vmax <5.0 m/s, 8.6%; and Vmax ≥5.0 m/s, 2.2% • **Median (IQR) logistic EuroSCORE**: 4.0 m/s ≤ Vmax <4.5 m/s, 7.9 (5.1-12.1)%; 4.5 ≤ Vmax <5.0 m/s, 7.2 (4.8-13.3)%; and Vmax ≥5.0 m/s, 8.7 (5.1-13.3)%

Reference	Nakatsuma 2017[188]
	• **Median (IQR) EuroSCORE II**: 4.0 m/s ≤ Vmax <4.5 m/s, 2.2 (1.4-3.2)%; 4.5 ≤ Vmax <5.0 m/s, 2.3 (1.3-3.7)%; and Vmax ≥5.0 m/s, 2.5 (1.4-3.5)% • **Median (IQR) STS score (PROM)**: 4.0 m/s ≤ Vmax <4.5 m/s, 3.2 (2.0-5.0)%; 4.5 ≤ Vmax <5.0 m/s, 3.1 (1.8-5.1)%; and Vmax ≥5.0 m/s, 3.3 (1.8-4.3)% • **Aetiology of aortic stenosis**: o Degenerative: 4.0 m/s ≤ Vmax <4.5 m/s, 89%; 4.5 ≤ Vmax <5.0 m/s, 83%; and Vmax ≥5.0 m/s, 85% o Congenital: 4.0 m/s ≤ Vmax <4.5 m/s, 6.3%; 4.5 ≤ Vmax <5.0 m/s, 11%; and Vmax ≥5.0 m/s, 8.7% o Rheumatic: 4.0 m/s ≤ Vmax <4.5 m/s, 3.6 %; 4.5 ≤ Vmax <5.0 m/s, 2.9%; and Vmax ≥5.0 m/s, 5.4% o Infective endocarditis: 4.0 m/s ≤ Vmax <4.5 m/s, 0%; 4.5 ≤ Vmax <5.0 m/s, 0.7%; and Vmax ≥5.0 m/s, 0% o Other: 4.0 m/s ≤ Vmax <4.5 m/s, 0.8%; 4.5 ≤ Vmax <5.0 m/s, 2.1%; and Vmax ≥5.0 m/s, 1.1% • **Mean (SD) left ventricular ejection fraction:** 4.0 m/s ≤ Vmax <4.5 m/s, 69.2 (7.8)%; 4.5 ≤ Vmax <5.0 m/s, 67.8 (6.9)%; and Vmax ≥5.0 m/s, 69.9 (8.1)% Population source: Consecutive patients matching inclusion criteria from retrospective registry across 27 centres in Japan between January 2003 and December 2011.
Prognostic variable	**In those treated conservatively with watchful waiting:** 4.0 m/s ≤ Vmax <4.5 m/s (referent) 4.5 ≤ Vmax <5.0 m/s Vmax ≥5.0 m/s Median follow-up duration of surviving patients in whole sample population was 1336 (IQR, 966-1817) days. Not reported separately for the asymptomatic subgroup.
Confounders/stratification strategy	A total of 19 clinically relevant risk-adjusting variables included in the model as confounders: age, male, BMI <22 kg/m^2, acute heart failure, hypertension, current smoking, diabetes mellitus on insulin therapy, past myocardial infarction, past symptomatic stroke, atrial fibrillation or flutter, aortic/peripheral vascular disease, haemodialysis, anaemia, liver cirrhosis, malignancy currently under treatment, chronic lung disease, left ventricular mass ≥181 g, any combined valvular disease and tricuspid regurgitation pressure gradient ≥40 mm Hg. Although, for some outcomes an analysis that also censored for surgical or transcatheter aortic valve replacement procedures during follow-up was also provided for the main analysis (asymptomatic and symptomatic), this was not provided for the asymptomatic subgroup. The centre was incorporated as a stratification variable.

Reference	Nakatsuma 2017[188]
Outcomes and effect sizes	**All-cause mortality** HR 1.34 (95% CI 0.94 to 1.92) for 4.5 ≤ Vmax <5.0 vs. 4.0 ≤ Vmax <4.5 **HR 1.23 (95% CI 0.83 to 1.82) for Vmax ≥5.0 vs. 4.0 ≤ Vmax <4.5** Cumulative incidence at 5 years: 39.4%, 45.4% and 54.0% for 4.0 ≤ Vmax <4.5, 4.5 ≤ Vmax <5.0 and Vmax ≥5.0, respectively. Number of patients with event during follow-up: 124, 58 and 42 for 4.0 ≤ Vmax <4.5, 4.5 ≤ Vmax <5.0 and Vmax ≥5.0, respectively. **Cardiovascular mortality** HR 1.27 (95% CI 0.79 to 2.03) for 4.5 ≤ Vmax <5.0 vs. 4.0 ≤ Vmax <4.5 **HR 1.43 (95% CI 0.88 to 2.33) for Vmax ≥5.0 vs. 4.0 ≤ Vmax <4.5** Cumulative incidence at 5 years: 27.5%, 32.0% and 45.5% for 4.0 ≤ Vmax <4.5, 4.5 ≤ Vmax <5.0 and Vmax ≥5.0, respectively. Number of patients with event during follow-up: 77, 36 and 30 for 4.0 ≤ Vmax <4.5, 4.5 ≤ Vmax <5.0 and Vmax ≥5.0, respectively. **Aortic valve-related mortality** HR 1.46 (95% CI 0.81 to 2.62) for 4.5 ≤ Vmax <5.0 vs. 4.0 ≤ Vmax <4.5 **HR 1.69 (95% CI 0.94 to 3.07) for Vmax ≥5.0 vs. 4.0 ≤ Vmax <4.5** Cumulative incidence at 5 years: 18.4%, 22.3% and 38.1% for 4.0 ≤ Vmax <4.5, 4.5 ≤ Vmax <5.0 and Vmax ≥5.0, respectively. Number of patients with event during follow-up: 47, 25 and 23 for 4.0 ≤ Vmax <4.5, 4.5 ≤ Vmax <5.0 and Vmax ≥5.0, respectively. **Heart failure hospitalisation** HR 1.19 (95% CI 0.73 to 1.94) for 4.5 ≤ Vmax <5.0 vs. 4.0 ≤ Vmax <4.5 **HR 1.65 (95% CI 0.97 to 2.83) for Vmax ≥5.0 vs. 4.0 ≤ Vmax <4.5** Cumulative incidence at 5 years: 22.8%, 30.3% and 41.0% for 4.0 ≤ Vmax <4.5, 4.5 ≤ Vmax <5.0 and Vmax ≥5.0, respectively. Number of patients with event during follow-up: 63, 33 and 27 for 4.0 ≤ Vmax <4.5, 4.5 ≤ Vmax <5.0 and Vmax ≥5.0, respectively. **Aortic valve-related mortality or heart failure hospitalisation composite** HR 1.31 (95% CI 0.86 to 1.99) for 4.5 ≤ Vmax <5.0 vs. 4.0 ≤ Vmax <4.5

Reference	Nakatsuma 2017[188]
	HR 1.59 (95% CI 1.01 to 2.52) for Vmax ≥5.0 vs. 4.0 ≤ Vmax <4.5 Cumulative incidence at 5 years: 29.4%, 38.9% and 47.7% for 4.0 ≤ Vmax <4.5, 4.5 ≤ Vmax <5.0 and Vmax ≥5.0, respectively. Number of patients with event during follow-up: 82, 45 and 35 for 4.0 ≤ Vmax <4.5, 4.5 ≤ Vmax <5.0 and Vmax ≥5.0, respectively.
Comments	**All-cause mortality** 1. Study participation — LOW 2. Study attrition — LOW 3. Prognostic factor measurement — LOW 4. Outcome Measurement — HIGH 5. Study confounding — LOW 6. Statistical analysis — LOW 7. Other risk of bias — HIGH OVERALL RISK OF BIAS — VERY HIGH **Cardiovascular mortality** 1. Study participation — LOW 2. Study attrition — LOW 3. Prognostic factor measurement — LOW 4. Outcome Measurement — HIGH 5. Study confounding — LOW 6. Statistical analysis — HIGH 7. Other risk of bias — HIGH OVERALL RISK OF BIAS — VERY HIGH **Aortic valve-related mortality** 1. Study participation — LOW 2. Study attrition — LOW 3. Prognostic factor measurement — LOW 4. Outcome Measurement — HIGH

Reference	Nakatsuma 2017[188]	
	5. Study confounding	LOW
	6. Statistical analysis	HIGH
	7. Other risk of bias	HIGH
	OVERALL RISK OF BIAS	VERY HIGH
	Heart failure hospitalisation	
	1. Study participation	LOW
	2. Study attrition	LOW
	3. Prognostic factor measurement	LOW
	4. Outcome Measurement	HIGH
	5. Study confounding	LOW
	6. Statistical analysis	HIGH
	7. Other risk of bias	HIGH
	OVERALL RISK OF BIAS	VERY HIGH
	Aortic valve-related death or heart failure hospitalisation composite	
	1. Study participation	LOW
	2. Study attrition	LOW
	3. Prognostic factor measurement	LOW
	4. Outcome Measurement	HIGH
	5. Study confounding	LOW
	6. Statistical analysis	HIGH
	7. Other risk of bias	HIGH
	OVERALL RISK OF BIAS	VERY HIGH
	Indirect: not a single threshold (above and below a certain value)	

1

2

Reference	Nakatsuma 2019[187]				
Study type and analysis	CURRENT AS registry: retrospective multicentre registry enrolling patients across 27 centres in Japan between January 2003 and December 2011. Multivariable Cox proportional hazards model				
Number of participants and characteristics	N=387 Patients were divided into groups according to BNP levels as follows. Group 1: BNP<100 pg/mL, n=201 (referent) Group 2: 100≤BNP<200 pg/mL, n=94 Group 3: 200≤BNP<300 pg/mL, n=42 Group 4: BNP≥300 pg/mL, n=50 **Inclusion criteria:** consecutive patients in the hospital database for transthoracic echocardiography meeting criteria for severe aortic stenosis [peak aortic jet velocity (Vmax) >4.0 m/s, mean aortic pressure gradient >40 mmHg or aortic valve area <1.0 cm^2] for the first time during the study period, who had no AS-related symptoms (angina, syncope and HF symptoms, including dyspnoea), were managed conservatively under watchful waiting at the time of diagnosis, and had BNP values obtained <180 days after index echo. **Exclusion criteria:** Symptom data not available (n=2), AVR selected as the initial treatment strategy after the index echocardiography (n=1196), haemodialysis (n=270), BNP values unknown (n=1313), BNP values were obtained ≥180 days after the index echocardiography (n=55), left ventricular ejection fraction (LVEF) of <50% (n=169), Vmax values of ≥5.0 m/s (n=118) and symptomatic patients (n=305).				
		Group 1	**Group 2**	**Group 3**	**Group 4**
	• **Mean (SD) age (years)**:	75.6 (8.9)	80.0 (8.4)	83.6 (8.1)	83.7 (8.3)
	• **Sex, male (%)**:	39	43	36	38
	• **Surgical AVR or TAVI (cumulative 5-year incidence, %)**	41.4	37.2	19.1	36.5
	• **Comorbid moderate or severe HVD**	19	39	45	25
	• **Co-morbid cardiac abnormalities (%)**:				
	○ Prior percutaneous coronary intervention	11	17	19	18
	○ Prior CABG	4.5	6.4	2.4	2.0
	○ Prior open heart surgery	12	8.5	2.4	4.0
	○ AF or flutter	13	35	38	34

Reference	Nakatsuma 2019[187]				
	○ Coronary artery disease	24	33	29	24
	○ EuroSCORE II	1.9	2.7	3.2	3.7
	○ STS score	2.7	3.4	4.4	4.3
	Aetiology of AS				
	○ Degenerative	85	89	95	94
	○ Congenital	9.5	5.3	2.4	2.0
	○ Rheumatic	5.5	5.3	2.4	2.0
	Population source: consecutive patients with severe AS enrolled in the CURRENT AS registry of 27 centres in Japan between January 2003 and December 2011 Median follow-up duration 1190 (IQR: 732-1540) days The follow-up data were mainly collected through review of hospital charts or through contact with the patients or their relatives and/or the referring physicians asking questions about survival status, symptoms and subsequent hospitalisation. Sudden death was defined as unexplained death in previously stable patients. Aortic valve-related death included aortic procedure-related death, sudden death and death due to HF that might have been related to AS. HF hospitalisation was defined as hospitalisation due to worsening HF that required intravenous drug therapy. The clinical event committee adjudicated the clinical events in a blinded fashion with respect to their BNP levels.				
Prognostic variables	Group 1: BNP<100 pg/mL, n=201 (referent) Group 2: 100≤BNP<200 pg/mL, n=94 Group 3: 200≤BNP<300 pg/mL, n=42 Group 4: BNP≥300 pg/mL, n=50				
Confounders	Four clinically relevant risk-adjusting non-cardiac variables (age, male sex, body mass index and the serum creatinine level), which were reported to affect the BNP level. Age, BMI and the serum creatinine level as continuous variables The centre was included as the stratification variable.				
Outcomes and effect sizes	**Composite of aortic valve-related death or hospitalization due to HF (cumulative 5- year incidence: number of events in groups 1, 2, 3 and 5: 25/201, 294, 14/42, 18/50)** HR 1.97 (0.97–3.98) for group 2 versus group 1 HR 3.59 (1.55–8.32) for group 3 versus group 1				

Reference	Nakatsuma 2019[187]	
	HR 7.38 (3.21–16.9) for group 4 versus group 1 Only univariate analysis for other outcomes	
Comments	1. Study participation 2. Study attrition 3. Prognostic factor measurement 4. Outcome Measurement 5. Study confounding 6. Statistical analysis 7. Other risk of bias OVERALL RISK OF BIAS Baseline difference for atrial fibrillation or flutter, higher serum creatinine levels and higher surgical risk scores. Not accounted for in analysis	HIGH LOW HIGH HIGH HIGH HIGH LOW VERY HIGH

1

Reference	Rosenhek 2000[219]
Study type and analysis	Prospective cohort study enrolling between 1st January and 31st December 1994. Multivariable Cox proportional hazards model.
Number of participants and characteristics	N=128 Aortic jet velocity (Vmax) ≥4.5 m/sec, n=64 Aortic jet velocity (Vmax) <4.5 m/sec, n=62 (n=2 were lost to follow-up so only 126 included in the multivariable analysis). **Inclusion criteria:** Stenotic native aortic valve with Vmax ≥4.0 m/sec; asymptomatic. **Exclusion criteria:** Additional haemodynamically significant valvular lesions; symptomatic (patients with mild fatigue or mild dyspnoea during maximal exercise were not excluded due to the non-specific nature of these symptoms).

Reference	Rosenhek 2000[219]
	• **Mean (SD) age**: 60 (18) years • **Sex**: 53.9% male • **Valve surgery**: n=22 patients received aortic valve replacement within 3 months of initial examination despite remaining asymptomatic. A further 59 valve replacements were performed during follow-up due to symptom development. • **Single vs multiple valve disease**: haemodynamically significant additional valve disease was excluded, however mild-moderate additional valve disease was present in a proportion of people, as follows: o Mild aortic regurgitation, 54.7% o Mid-moderate or moderate aortic regurgitation, 25.8% o Mild mitral regurgitation, 65.6% o Mild tricuspid regurgitation, 47.7% o Mild mitral stenosis, 6.3% • **Co-morbid cardiac abnormalities**: o Hypertension, 34.4% o Coronary artery disease, 25.8% o Mitral annular calcification, 36.7% • **Mean (SD) aortic valve area**: 0.68 (0.11) cm^2 • **Mean (SD) Vmax**: 5.0 (0.6) m/sec • **Left ventricular function**: all but 2 patients had normal left ventricular function Population source: consecutive patients matching inclusion criteria at single echocardiography laboratory between 1st January and 31st December 1994.
Prognostic variable	**Mixture of those that were treated conservatively and those that received surgery:** overall, the approach was to only offer surgery once symptoms developed, though n=22 received surgery before symptoms developed, within three months of the initial examination, at the discretion of the physician. These patients were censored from the analysis at the time of aortic valve replacement. Vmax ≥4.5 m/sec Vmax <4.5 m/sec (referent) Mean follow-up was 22±18 months (range, 0 to 54 months). Follow-up information was available for 126/128 patients (98%).

Reference	Rosenhek 2000[219]
Confounders	The following factors were included as part of the multivariate analysis: age, sex, coronary artery disease, hypertension, diabetes, hypercholesterolaemia, degree of aortic valve calcification and aortic jet velocity. Cause of stenosis also mentioned in methods section but does not appear in the multivariate analysis table, so assume not included in the multivariate analysis.
Outcomes and effect sizes	**Death or aortic valve replacement indication due to the development of symptoms** **RR 1.1 (0.7 to 1.9) for Vmax ≥4.5 vs. <4.5 m/sec** During follow-up, 67 end-points were reached (n=8 deaths and n=59 aortic valve replacements due to development of symptoms). A further 22 patients were operated on before symptoms developed as discretion of physician, but these were censored from the analysis. Event-free survival was 67±5% at 1 year, 56±5% at 2 years and 33±5 % at 4 years. N=6 deaths were cardiac-related (n=4 due to congestive heart failure, n=1 due to endocarditis and n=1 sudden death). Apart from the sudden death, all were preceded by symptoms. However, aortic valve replacement was not performed due to patient refusal in 3 cases, advanced prostate cancer in 1 patient and a further patient died while waiting for surgery. Of the 2 non-cardiac deaths, n=1 was due to pulmonary embolism and n=1 was due to acute myeloid leukaemia. Of the 59 patients that underwent aortic valve replacement following symptom development, n=5 deaths occurred. Four of these deaths occurred perioperatively and one was non-cardiac-related. The remaining 54 patients were alive at the end of the study in 1998 Overall actuarial survival at the end of the study in 1998 was 93±2% at 1 year, 91±3 at 2 years and 87±3% at 4 years.
Comments	1. Study participation HIGH 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement HIGH 5. Study confounding LOW 6. Statistical analysis HIGH 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH Potential prognostic factor indirectness: threshold does not match any of the two thresholds specified in the protocol. Potential outcome indirectness: composite outcome of two outcomes, one of which pre-specified in the protocol.

Reference	Rosenhek 2010[223]
Study type and analysis	Prospective cohort study of those in single outpatient clinic for heart valve disease between 1995 and 2008 Multivariable Cox proportional hazards model
Number of participants and characteristics	N=116 <u>Analysis 1</u> Peak aortic jet velocity (Vmax) 5.0 to 5.5 m/s, n=72 Peak aortic jet velocity (Vmax) ≥5.5 m/s, n=44 <u>Analysis 2</u> Aortic valve area <0.6 cm^2, n=47 Aortic valve area ≥0.6 cm^2, n=69 **Inclusion criteria:** Patients examined in outpatient clinic for valvular heart disease between 1995 and 2008 with: stenotic aortic valve and peak aortic jet velocity ≥5.0 m/s. **Exclusion criteria:** Additional haemodynamically significant valve lesions (moderate or severe) or presence of symptoms. Values below are provided for the whole cohort with the data for the two peak aortic jet velocity subgroups provided separately. Characteristics were not reported in the study for each of the aortic valve area subgroups. • **Mean (SD) age**: 67 (15) years – 67 (15) and 66 (15) years for the Vmax 5.0 to 5.5 m/s and Vmax ≥5.5 m/s groups, respectively. • **Sex**: 51% male – 51% and 50% male for the Vmax 5.0 to 5.5 m/s and Vmax ≥5.5 m/s groups, respectively. • **Valve surgery**: Aortic valve replacement indicated in 9116 patients during follow-up. A total of 79 patients underwent replacement, 10 patients refused surgery and 1 was awaiting surgery at time of report. • **Single vs multiple valve disease**: Additional mild or mild-moderate valve disease present in some patients: ○ Mild aortic regurgitation, 41.4%

Reference	Rosenhek 2010[223]
	○ Mild-moderate aortic regurgitation, 9.5% ○ Mild mitral regurgitation, 41.4% ○ Mild-moderate mitral regurgitation, 15.5% ○ Mild tricuspid regurgitation, 42.2% ○ Mild mitral stenosis, 2.6% • **Co-morbid cardiac abnormalities**: ○ Hypertension, 56% - 53% and 61% for the Vmax 5.0 to 5.5 m/s and Vmax ≥5.5 m/s groups, respectively. ○ Coronary artery disease, 22% - 21% and 25% for the Vmax 5.0 to 5.5 m/s and Vmax ≥5.5 m/s groups, respectively. Population source: All patients examined in outpatient clinic between 1995 and 2008 matching inclusion criteria.
Prognostic variables	**In those treated conservatively with watchful waiting:** This isn't very explicit in the paper but appears that all would have been treated conservatively and followed up for signs that may indicate referral for surgery was required. <u>Analysis 1</u> Peak aortic jet velocity (Vmax) 5.0 to 5.5 m/s (referent) Peak aortic jet velocity (Vmax) ≥5.5 m/s <u>Analysis 2</u> Aortic valve area <0.6 cm^2 Aortic valve area ≥0.6 cm^2 (referent) Median (IQR) follow-up during the study was 41 (26-63) months. Follow-up information was complete for 113 patients (97.4%).
Confounders	Age >70 years, sex, coronary artery disease, hypertension, diabetes mellitus, hypercholesterolaemia, aortic valve area <0.6 cm^2, aortic valve peak velocity ≥5.5 m/s were included in the multivariable analysis.
Outcomes and effect sizes	**Cardiac mortality or indication for aortic valve replacement** <u>Analysis 1:</u> **HR 1.88 (95% CI 1.19 to 2.96) for Vmax ≥5.5 m/s vs. Vmax 5.0 to 5.5 m/s** Event-free survival rates at 1, 2, 3 and 4 years, respectively, were as follows: • 76±5%, 43±6%, 33±6% and 17±5% for the Vmax 5.0 to 5.5 m/s group (n=72) • 44±8%, 27±7%, 11±5% and 4±4% for the Vmax ≥5.5 m/s group (n=44) – P<0.0001 vs. Vmax 5.0 to 5.5 m/s group

Reference	Rosenhek 2010[223]
	Analysis 2: **HR 1.25 (95% CI 0.77 to 2.02) for aortic valve area <0.6 cm^2 vs. ≥0.6 cm^2** The outcome of patients with an aortic valve area <0.6 cm^2 was not significantly different from the outcome of those with a valve area ≥0.6 cm^2. P=0.12.
Comments	**Analysis 1** 1. Study participation LOW 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement HIGH 5. Study confounding LOW 6. Statistical analysis LOW 7. Other risk of bias LOW OVERALL RISK OF BIAS HIGH Potential outcome indirectness: composite of cardiac mortality and indication for aortic valve replacement **Analysis 2** 1. Study participation LOW 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement HIGH 5. Study confounding LOW 6. Statistical analysis LOW 7. Other risk of bias LOW OVERALL RISK OF BIAS HIGH Potential outcome indirectness: composite of cardiac mortality and indication for aortic valve replacement

Reference	Saito 2012[229]
Study type and analysis	Retrospective cohort of those between 2001 and 2007 matching inclusion criteria at single site.

Reference	Saito 2012[229]
	Multivariable Cox proportional hazards model.
Number of participants and characteristics	N=103 Analysis 1 Aortic valve area index (AVAI) <0.6 cm^2/m^2, n=66 Aortic valve area index (AVAI) ≥0.6 cm^2/m^2, n=37 Analysis 2 Aortic valve area <0.75 cm^2, number not reported Aortic valve area ≥0.75 cm^2, number not reported Analysis 3 Peak aortic jet velocity (Vmax) >4.0 m/s, n=58 Peak aortic jet velocity (Vmax) ≤4.0 m/s, n=45 **Inclusion criteria:** Asymptomatic patients who underwent transthoracic echocardiography and had severe aortic stenosis, defined as aortic valve area <1.0 cm^2; had not undergone aortic valve replacement on initial evaluation. **Exclusion criteria:** History of coronary artery disease; more than mild mitral valve regurgitation or stenosis; more than mild aortic regurgitation; primary hypertrophic cardiomyopathy; those with planned aortic valve replacement at initial evaluation; and symptoms associated with aortic stenosis. Values below are provided for the whole cohort with the data for the two aortic valve area index subgroups provided separately. Characteristics were not reported in the study for each of the aortic valve area or peak aortic jet velocity subgroups. • **Mean (SD) age**: 72 (11) years – 72 (11) and 73 (11) years for the AVAI <0.6 cm^2/m^2 and AVAI ≥0.6 cm^2/m^2 groups, respectively. • **Sex**: 45% male – 47% and 41% for the AVAI <0.6 cm^2/m^2 and AVAI ≥0.6 cm^2/m^2 groups, respectively. • **Valve surgery**: 31/103 underwent aortic valve replacement during the follow-up period. • **Single vs multiple valve disease**: Not reported. • **Co-morbid cardiac abnormalities**:

Reference	Saito 2012[229]
	○ Hypertension, 55% - 53% and 59% for the AVAI <0.6 cm^2/m^2 and AVAI ≥0.6 cm^2/m^2 groups, respectively. ○ Atrial fibrillation, 13% - 17% and 5% for the AVAI <0.6 cm^2/m^2 and AVAI ≥0.6 cm^2/m^2 groups, respectively. • **Mean (SD) left ventricular ejection fraction:** 60.0 (9.6)% – 59.6 (9.9)% and 60.7 (9.0)% for the AVAI <0.6 cm^2/m^2 and AVAI ≥0.6 cm^2/m^2 groups, respectively. Population source: retrospective review of patients from single site between 2001 and 2007. Unclear if consecutive.
Prognostic variables	**In those treated conservatively at initial evaluation:** <u>Analysis 1</u> Aortic valve area index (AVAI) <0.6 cm^2/m^2 Aortic valve area index (AVAI) ≥0.6 cm^2/m^2 (referent) <u>Analysis 2</u> Aortic valve area <0.75 cm^2 Aortic valve area ≥0.75 cm^2 (referent) <u>Analysis 3 [not analysed in review as evidence available for protocol threshold]</u> Peak aortic jet velocity (Vmax) >4.0 m/s Peak aortic jet velocity (Vmax) ≤4.0 m/s (referent) Mean (SD) follow-up was 36 (27) months.
Confounders	Only the following three variables were included in the multivariate analysis: AVAI <0.6 cm^2/m^2, aortic valve area <0.75 cm^2 and peak aortic jet velocity (Vmax) >4.0 m/s. The following variables were assessed on univariate analysis: age, sex, AVAI <0.6 cm^2/m^2, peak aortic jet velocity >4.0 m/s, aortic valve area <0.75 cm^2, left ventricular ejection fraction (%, continuous), left ventricular mass index (g/m^2, continuous), E/e' >15, heart rate (continuous), hypertension, dyslipidaemia, diabetes mellitus, haemodialysis, serum creatinine (mg/dl, continuous), C-reactive protein (mg/dl, continuous), but only the three variables with P-values <0.05 on univariate analysis were incorporated into the multivariate model, as detailed above.
Outcomes and effect sizes	**Cardiovascular mortality or aortic valve replacement**

Reference	Saito 2012[229]
	During follow-up, 51 events occurred (including 31 aortic valve replacements and 20 cardiac deaths). Event-free survival rate for all patients was 81%, 74%, 58% and 48%, respectively, at 1, 2, 3 and 5 years. Those undergoing aortic valve replacements did so due to: development of symptoms (n=24) or decreased left ventricular systolic function (n=7). The 20 cardiac-related deaths were due to: congestive heart failure (n=14) and sudden death (n=6). Four patients that experienced sudden death had developed symptoms beforehand but did not undergo aortic valve replacement due to old age or substantial comorbidities. Analysis 1 **HR 2.62 (95% CI 1.09 to 6.33) for AVAI <0.6 cm^2/m^2 vs. AVAI ≥0.6 cm^2/m^2** Event-free survival rates at 1, 2, 3 and 5 years were as follows: ○ 100%, 97%, 86% and 71% for the AVAI ≥0.6 cm^2/m^2 group ○ 71%, 60%, 41% and 35% for the AVAI <0.6 cm^2/m^2 group Analysis 2 **HR 1.48 (95% CI 0.79 to 2.79) for aortic valve area <0.75 cm^2 vs. ≥0.75 cm^2** Event-free survival rates not reported at 1, 2, 3 and 5 years for this prognostic variable. Analysis 3 **HR 2.58 (95% CI 1.15 to 5.78) for Vmax >4.0 m/s vs. Vmax ≤4.0 m/s** Event-free survival rates at 1, 2, 3 and 5 years were as follows: ○ 93%, 86%, 79% and 74% for the Vmax ≤4.0 m/s group ○ 72%, 65%, 43% and 31% for the Vmax >4.0 m/s group
Comments	**Analysis 1** 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

Reference	Saito 2012[229]
	Potential outcome indirectness: composite of cardiovascular mortality and aortic valve replacement Potential prognostic factor indirectness: AVAI (AVA corrected for BSA) not a factor that we had pre-specified in protocol but similar to aortic valve area which is pre-specified **Analysis 2** 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 Potential outcome indirectness: composite of cardiovascular mortality and aortic valve replacement Potential prognostic factor indirectness: not the threshold for this factor that we had pre-specified (<0.75 cm^2 rather than <0.6 cm^2) **Analysis 3** 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 Potential outcome indirectness: composite of cardiovascular mortality and aortic valve replacement

Reference	Saito 2012[229]
	Potential prognostic factor indirectness: not the threshold for this factor that we had pre-specified (>0.4 m/s rather than >5.0 or >5.5 m/s)

1

Reference	Taniguchi 2018[244]
Study type and analysis	CURRENT AS registry: retrospective multicentre registry enrolling patients across 27 centres in Japan between January 2003 and December 2011. Multivariable logistic regression model.
Number of participants and characteristics	N=1808 in the asymptomatic subgroup, n=291 managed with initial aortic valve replacement strategy and n=1517 managed with initial conservative strategy (n=3815 in total study population). <u>Analysis 1</u> Vmax ≥5 m/s, n=207 Vmax <5 m/s, n=1601 <u>Analysis 2</u> LVEF <60%, n=355 LVEF ≥60%, n=1453 **Inclusion criteria:** Those meeting criteria for severe aortic stenosis [peak aortic jet velocity (Vmax) >4.0 m/s, mean aortic pressure gradient >40 mmHg or aortic valve area <1.0 cm^2] for the first time during the study period Note: the study includes those with both symptomatic and asymptomatic severe AS and provides data for each of these two groups separately. Only the asymptomatic group was included in this review as per the protocol. **Exclusion criteria:** Limited information regarding exclusion criteria. Two patients had unclear symptomatic status and so these were not included in the analysis of subgroups based on symptomatic status (asymptomatic and symptomatic). Note: all below information is for the asymptomatic subgroup

Reference	Taniguchi 2018[244]
	• **Mean (SD) age**: 76.8 (9.6) years • **Sex**: 40% male • **Valve surgery**: Number eventually receiving aortic valve replacement/surgery during follow-up not reported • **Single vs multiple valve disease**: any combined valvular disease (moderate or severe): o Moderate or severe aortic regurgitation, 16% o Moderate or severe mitral stenosis, 3% o Moderate or severe mitral regurgitation, 12% o Moderate or severe tricuspid regurgitation, 12% • **Co-morbid cardiac abnormalities**: o Hypertension, 69% o Coronary artery disease, 27% o Atrial fibrillation or flutter, 19% o Aortic/peripheral vascular disease, 9% • **Past open heart surgery**: 9% • **Median (IQR) logistic EuroSCORE:** 8.4 (5.1-13.9)% • **Median (IQR) EuroSCORE II:** 2.4 (1.4-3.6)% • **Median (IQR) STS score (PROM)**: 3.3 (2.0-5.2)% • **Left ventricular ejection fraction <50% and <60%**: 8% and 20%, respectively • **Initial treatment strategy**: o Initial aortic valve replacement strategy: 291/1808 (16%) o Initial conservative strategy: 1517/1809 (84%) Population source: Consecutive patients matching inclusion criteria from retrospective registry across 27 centres in Japan between January 2003 and December 2011.
Prognostic variables	**Mixture of those that received conservative management and those that had aortic valve replacement planned following initial evaluation –** however, patients that received transcatheter or surgical aortic valve replacement were censored from the analysis at the time of operation <u>Analysis 1</u> Vmax ≥5 m/s Vmax <5 m/s (referent)

Reference	Taniguchi 2018[244]
	<u>Analysis 2</u> LVEF <60% LVEF ≥60% (referent) Median follow-up of surviving patients in the entire cohort was 1334 (IQR, 1019-1701) days. Not specified for the asymptomatic subgroup. There was a 93% follow-up rate at 2 years. Patients were censored at time of TAVI or surgical AVR, so the analysis follow up until they are no longer being treated conservatively
Confounders/stratification strategy	The following 10 clinically relevant risk-adjusting variables included in the model as confounders for the asymptomatic subgroup: Vmax ≥5 m/s, LVEF <60%, age ≥80 years, male, BMI <22 kg/m^2, past myocardial infarction, atrial fibrillation or flutter, haemodialysis, malignancy currently under treatment and any combined valvular disease The above 10 factors were selected from a total of 20 performed on the whole cohort group, as the number of events in the subgroups was lower and the same number of factors could therefore not be incorporated. They were selected based on those that suggested strong involvement in the whole cohort analysis. Multivariate model developed to identify characteristics associated with an increased risk of sudden death, with censoring at surgical or transcatheter aortic valve replacement in the entire cohort. The model also accounted for the competing risk of death other than sudden death. The centre was incorporated as a stratification variable.
Outcomes and effect sizes	**Sudden death** There were 82 sudden deaths among those with no symptoms at baseline – of these, 54 died abruptly with no preceding symptoms and 35 died with no symptoms within 3 months of the last clinical follow-up. Cumulative 5-year incidence of sudden death was 7.2% in asymptomatic group (5.8% without censoring for surgical or transcatheter aortic valve replacement). <u>Analysis 1</u> **HR 2.36 (95% CI 1.09 to 5.14) for Vmax ≥5 m/s vs. Vmax <5 m/s** <u>Analysis 2</u> **HR 1.76 (95% CI 1.08 to 2.87) for LVEF <60% vs. LVEF ≥60%**

Reference	Taniguchi 2018[244]	
Comments	**Analysis 1**	
	1. Study participation	LOW
	2. Study attrition	LOW
	3. Prognostic factor measurement	LOW
	4. Outcome Measurement	HIGH
	5. Study confounding	LOW
	6. Statistical analysis	HIGH
	7. Other risk of bias	LOW
	OVERALL RISK OF BIAS	VERY HIGH
	Analysis 2	
	1. Study participation	LOW
	2. Study attrition	LOW
	3. Prognostic factor measurement	LOW
	4. Outcome Measurement	HIGH
	5. Study confounding	LOW
	6. Statistical analysis	HIGH
	7. Other risk of bias	LOW
	OVERALL RISK OF BIAS	VERY HIGH

Reference	Thellier 2020[253]
Study type and analysis	Retrospective cohort study of those in single echo lab between 2011 and 2018 recorded in a prospective registry Multivariable Cox proportional hazards model and propensity matched analysis
Number of participants and characteristics	N=332 LV-GLS ≤15 (n=192, 98 in matched cohort) LV-GLS >15 (n=140, 98 in matched cohort) (referent) **Inclusion criteria:**

Reference	Thellier 2020[253]

	Age 18 years or over with diagnosed severe AS (AVA ≤1 cm^2 and/or AVAi ≤0.6 cm/m^2) with no or mild AS-related symptoms and preserved LVEF ≥50%
	
	Exclusion criteria:
	Additional moderate or greater aortic, mitral or tricuspid regurgitation; past or current NYHA class III-IV heart failure, angina or syncope, prosthetic valve or supra- or sub-valvular AS, congenital heart disease or dynamic LVOT obstruction, mitral stenosis or refusal to participate.
	
	• **Median (IQR) age**: 79 (71-85) years
	• **Sex**: 41% male
	• **NYHA class I**: 58%
	• **Co-morbid cardiac abnormalities**:
	  ○ Hypertension, 71%
	  ○ Atrial fibrillation, 29%
	  ○ Coronary artery disease, 23%
	• **Median (IQR) left ventricular ejection fraction:** 61 (57-66)%
	• **Mean (SD) GLS:** 13.8 (4.1)%
	
	Population source: consecutive patients from single echo lab.

Prognostic variable	LV-GLS ≤15 LV-GLS >15 (referent) Median follow-up 42 (IQR: 37-46) months Reproducibility of GLS assessment: intra-observer ICC = 0.95 (0.86-0.98); inter-observer ICC = 0.93 (0.83-0.97)
Confounders	Multivariate model 1: age, sex, Charlson comorbidity index, CAD, hypertension, AF, BMI and AVR as a time-dependent variable. Multivariate model 2: echocardiographic AVA, LVH, LAVi ≥34ml/m^2, sPAP >60 mmHg, E/e' >14, RV dysfunction, LVEF <60% and LV SVi <30 ml/m^2 and AVR as a time-dependent variable. Multivariate model 3: age, sex, Charlson comorbidity index, CAD, hypertension, AF, BMI, AVA, LV SVi <30 ml/m^2, LVEF <60% and AVR as a time-dependent variable.

Reference	Thellier 2020[253]
	Propensity matching for: age, sex, AF, comorbidity, AVA, LV SVi, LVEF, RV dysfunction.
Outcomes and effect sizes	**Mortality (model 1)** **HR 2.07 (95% CI 1.23 to 3.49) for** LV-GLS ≤15 **vs. >15%** **Mortality (model 2)** **HR 2.63 (95% CI 1.53 to 4.50) for** LV-GLS ≤15 **vs. >15%** **Mortality (model 3)** **HR 1.99 (95% CI 1.17 to 3.38) for** LV-GLS ≤15 **vs. >15%** **Mortality in propensity matched cohort** **HR 2.10 (95% CI 1.20 to 3.68) for** LV-GLS ≤15 **vs. >15%** A total of 123 AVRs and 105 deaths occurred.
Comments	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 Prognostic factor indirectness: threshold does not match protocol Population indirectness: includes people with mild AS-related symptoms

Reference	Zilberszac 2017[281]
Study type and analysis	Prospective cohort study of those in single outpatient clinic for heart valve disease between 1999 and 2009 Multivariable Cox proportional hazards model
Number of participants and characteristics	N=103 Peak aortic jet velocity (Vmax) ≥5.0 m/s, n=39 Peak aortic jet velocity (Vmax) between 4.0 and 5.0 m/s, n=64 **Inclusion criteria:** >70 years of age studied at outpatient clinic between 1999 and 2009; stenotic native aortic valve with a peak aortic jet velocity ≥4.0 m/s; asymptomatic; normal ejection fraction (≥55%). **Exclusion criteria:** Additional haemodynamically significant valve lesions (moderate-severe or severe); history of previous cardiac surgery. • **Mean (SD) age**: 77.3 (4.8) years • **Sex**: 50% male • **Valve surgery**: During follow-up, aortic valve surgery was indicated in 82/103 patients. At end of study, 71 underwent conventional aortic valve replacement and 11 refused surgery. • **Single vs multiple valve disease**: o Mild aortic regurgitation, 53.4% o Mild mitral regurgitation, 63.1% o Mild tricuspid regurgitation, 49.5% o Mild mitral stenosis, 1.9% • **Co-morbid cardiac abnormalities**: o Hypertension, 77% o Atrial fibrillation, 7% o Coronary artery disease, 30% o Peripheral artery disease, 12% • **Mean (SD) left ventricular ejection fraction:** 61.0 (5.9)%

Reference	Zilberszac 2017[281]
	• **Mean (SD) baseline logistic EuroSCORE:** 7.2 (4.1)% • **Mean (SD) baseline EuroSCORE II:** 2.7 (1.9)% Population source: consecutive patients from single outpatient clinic between 1999 and 2009. Majority referred from outpatient care specialists in internal medicine and general cardiologists. Note this is focused on the elderly population.
Prognostic variable	**In those receiving conservative management initially:** Vmax ≥5.0 m/s ≥4.0 Vmax <5.0 m/s (referent) Median potential follow-up was 19.4 (IQR, 9.8-36.4) months. Follow-up information was complete for 96/103 patients. Of those lost to follow-up, 2 were lost to follow-up while still asymptomatic and 5 following aortic valve replacement.
Confounders	Vmax ≥5.0 m/s, aortic valve area (continuous), age (continuous), aortic valve calcification, hypertension, hypercholesterolaemia, diabetes and coronary artery disease were included in the multivariable analysis.
Outcomes and effect sizes	**Cardiac mortality or indication for aortic valve replacement** **HR 1.93 (95% CI 1.16 to 3.23) for Vmax ≥5.0 m/s vs. ≥4.0 Vmax <5.0 m/s** A total of 91 events observed during the follow-up, including indication for aortic valve replacement in 82 patients (n=76 due to symptom development, n=3 due to severe aortic valve calcification, n=2 due to reduced left ventricular ejection fraction and n=1 undergoing major non-cardiac surgery in an asymptomatic patient) and cardiac mortality in 9 patients. Estimated event-free survival (with 95% CIs) at 1, 2, 3 and 4 years for the whole cohort was 73 (63-80)%, 43 (34-53)%, 23 (16-33)% and 16 (10-25)%, respectively. Estimated event-free survival (with 95% CIs) at 1, 2, 3 and 4 years, respectively, was as follows for the two Vmax groups: ○ 84 (73-91)%, 57 (44-68)%, 32 (21-44)% and 23 (14-35)% for the ≥4.0 Vmax <5.0 m/s group ○ 54 (38-69)%, 21 (11-36)%, 9 (3-24)% and 6 (2-21)% for the Vmax ≥5.0 m/s group
Comments	1. Study participation HIGH 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement HIGH 5. Study confounding LOW

Reference	Zilberszac 2017[281]	
	6. Statistical analysis	LOW
	7. Other risk of bias	LOW
	OVERALL RISK OF BIAS	VERY HIGH
	Potential outcome indirectness: composite of cardiac mortality and indication for aortic valve replacement	

D.2 Aortic regurgitation

Reference	de Meester 2019[64]
Study type and analysis	Retrospective review of prospectively completed database Multivariate Cox proportional hazards model
Number of participants and characteristics	N=356 (whole cohort, number that were asymptomatic unclear) <u>Analysis 1</u> Left ventricular ejection fraction (LVEF) <55%, number not reported Left ventricular ejection fraction (LVEF) ≥55%, number not reported <u>Analysis 2</u> Left ventricular end-systolic dimension/body surface area (LVESD/BSA) >22 mm/m^2, number not reported Left ventricular end-systolic dimension/body surface area (LVESD/BSA) ≤22 mm/m^2, number not reported **Inclusion criteria:** Severe (grade ≥3) aortic regurgitation diagnosed by Doppler echocardiography; operated on at the Cliniques Universitaires St-Luc in Brussels between 1st January 1995 and 31st December 2014. **Exclusion criteria:**

Reference	de Meester 2019[64]
	<18 years old; severe acute aortic regurgitation due to aortic dissection or endocarditis; concomitant severe mitral regurgitation or aortic stenosis; a non-dilated left ventricle (defined as left ventricular end-diastolic dimension <32 mm/m); previous valve surgery; glomerular filtration rate <30 ml/min; life expectancy <1 year. Note this is for the whole cohort, not for the asymptomatic subgroup, as these details were not provided. • **Mean (SD) age**: 51.21 (15.5) years • **Sex**: 83.1% male • **Valve surgery**: all underwent some form of surgery for aortic regurgitation to be enrolled in this study. Operative procedures consisted of aortic valve repair (80%), Ross procedure (7%), bioprosthetic aortic valve replacement (9%) and mechanical aortic valve replacement (4%). • **Single vs multiple valve disease**: unclear whether any concomitant mild valve disease. Severe mitral regurgitation and aortic stenosis were exclusion criteria. • **Co-morbid cardiac abnormalities**: o Atrial fibrillation, 14.6% o Hypertension, 47.8% o Peripheral artery disease, 2.2% • **Aortic pathology**: o Bicuspid valve, 43.0% o Type I dysfunction, 29.5% o Type II dysfunction, 46.3% o Type III dysfunction, 24.2% • **Associated coronary artery bypass grafting performed**: 8.4% • **Mean (SD) STS PROM score**: 1.02 (0.89) • **Prior percutaneous coronary intervention or coronary artery bypass grafting**: 0.6% • **Mean (SD) left ventricular ejection fraction:** 55.21 (10.08)% • **Mean (SD) left ventricular end-diastolic diameter:** 64.93 (7.115) mm • **Mean (SD) left ventricular end-systolic diameter:** 44.67 (7.051) mm Population source: consecutive patients with severe aortic regurgitation who were operated on between 1st January 1995 and 31st December 2014 at single centre.
Prognostic variables	**In those treated with valve intervention, asymptomatic subgroup:** Operative procedures consisted of aortic valve repair (80%), Ross procedure (7%), bioprosthetic aortic valve replacement (9%) and mechanical aortic valve replacement (4%).

Reference	de Meester 2019[64]
	<u>Analysis 1</u> LVEF <55% LVEF ≥55% (referent) <u>Analysis 2</u> LVESD >22 mm/m^2 LVESD/BSA ≤22 mm/m^2 (referent) Follow-up events were obtained for patients between September and December 2016. Median (range) follow-up was 8 (0.1 to 21.8) years.
Confounders	Inverse probability weights (IPW) were calculated, which allowed comparable patient cohorts to be obtained by weighing individual patients according to mismatched characteristics. Propensity scores included the following 10 covariates: age, sex, hypertension, chronic obstructive pulmonary disease, glomerular filtration rate >60 ml/min/1.73 m^2, bicuspid aortic valve, type I and type II aortic regurgitation, history of stroke and history of atrial fibrillation. These IPWs were then used within the Cox multivariate model to obtain unbiased estimates of hazards.
Outcomes and effect sizes	**Cardiovascular mortality or heart failure** <u>Analysis 1</u> **HR 4.13 (95% CI 1.65 to 10.33) for LVEF <55% vs. LVEF ≥55%** <u>Analysis 2</u> **HR 2.46 (95% CI 1.07 to 5.70) for LVESD >22 mm/m^2 vs. LVESD/BSA ≤22 mm/m^2**
Comments	**Analysis 1** 1. Study participation HIGH 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement HIGH 5. Study confounding LOW

Reference	de Meester 2019[64]
	6. Statistical analysis HIGH 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH Potential prognostic factor indirectness: threshold used is different to that specified in protocol Potential outcome indirectness: composite of two end-points listed in the protocol **Analysis 2** 1. Study participation HIGH 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement HIGH 5. Study confounding LOW 6. Statistical analysis HIGH 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH Potential prognostic factor indirectness: threshold used is different to that specified in protocol Potential outcome indirectness: composite of two end-points listed in the protocol

1

Reference	Maeda 2019[156]
Study type and analysis	Retrospective cohort study Multivariable Cox proportional hazards model
Number of participants and characteristics	N=162 <u>Analysis 1 – whole cohort</u> Indexed end-systolic diameter (ESDI) ≤25 mm/m^2 **AND** end-diastolic diameter (EDD) ≤65 mm, n=61 (referred to as early stage C in paper)

Reference	Maeda 2019[156]

	Indexed end-systolic diameter (ESDI) >25 mm/m^2 **OR** end-diastolic diameter (EDD) >65 mm, n=101 (referred to as late stage C in paper)
	(this group includes 59/101 with EDD >65 mm and 86/101 with ESDI >25 mm/m^2 – some with one or both)
	
	<u>Analysis 2 – those that survived >10 years post-aortic valve replacement (n=74)</u>
	ESDI ≤25 mm/m^2 **AND** end-diastolic diameter (EDD) ≤65 mm, n=25 (referred to as early stage C in paper)
	ESDI >25 mm/m^2 **OR** end-diastolic diameter (EDD) >65 mm, n=49 (referred to as late stage C in paper)
	(this group includes 32/49 with EDD >65 mm and 43/49 with ESDI >25 mm/m^2 – some with one or both)
	
	Inclusion criteria:
	Asymptomatic, chronic severe aortic regurgitation that underwent isolated aortic valve replacement for pure aortic regurgitation between January 1991 and December 2010; normal left ventricular ejection fraction (≥55%); end-systolic diameter ≤55 mm at rest; no history of hospitalisation for heart failure.
	
	Exclusion criteria:
	Aortic stenosis; mitral regurgitation or stenosis; significant coronary artery stenosis; infectious endocarditis; aortitis; missing data regarding preoperative echocardiographic findings or symptoms.
	
	Values below are given as the whole cohort followed by the values in each of the two subgroups based on left ventricular dimensions
	• **Mean (SD) age**: 59 (14) years – 58 (15) years vs. 59 (14) years
	• **Sex**: 76% male – 85% male vs. 70% male
	• **Valve surgery**: all underwent aortic valve replacement prior to follow-up.
	• **Single vs multiple valve disease**: not reported. Aortic stenosis, mitral regurgitation and mitral stenosis were exclusion criteria.
	• **Co-morbid cardiac abnormalities**:
	  ○ Atrial fibrillation, 7.4% - 7% vs. 8%
	  ○ Hypertension, 64.8% - 67% vs. 63%
	• **Mean (SD) left ventricular ejection fraction:** 64.26 (8.51)% - 68 (8)% vs. 62 (8)%
	• **Mean (SD) left ventricular end-diastolic diameter**: 62.74 (6.96) mm **-** 59 (5) vs. 65 (7) mm
	• **Mean (SD) left ventricular end-systolic diameter**: 41.74 (5.48) mm – 38 (4) vs. 44 (5) mm
	• **Mean (SD) left ventricular indexed end-systolic diameter**: 25.74 (4.47) mm/m^2 – 22 (2) vs. 28 (4) mm/m^2
	• **Mechanical prosthesis**: 62.3% - 66% vs. 60%

Reference	Maeda 2019[156]
	Population source: consecutive patients undergoing isolated aortic valve replacement for severe chronic pure aortic regurgitation across 5 different but associated institutions between January 1991 and December 2010.
Prognostic variables	**In those treated with aortic valve replacement:** For analyses 1 and 2 ESDI ≤25 mm/m^2 **AND** EDD ≤65 mm (referent) – also referred to as early stage C in paper ESDI >25 mm/m^2 **OR** EDD >65 mm – also referred to as late stage C in paper Mean (SD) follow-up was 9.9 (5.3) years (range, 0-23 years). A total of 7 patients were lost to follow-up so there was 96% complete follow-up.
Confounders	The following variables were included in the multivariate analysis: age, gender, diabetes mellitus, chronic kidney disease and late stage C (based on classification of left ventricular dimensions, as described in the prognostic factor groups). Factors that are clinically considered to affect survival were included in the multivariate analysis – no mention of univariate analyses being used to select these.
Outcomes and effect sizes	**All-cause mortality (late death)**: unclear what 'late death' is referring to, but may mean death that was not in-hospital as they list in-hospital deaths separately. Analysis 1 – whole cohort **HR 1.99 (95% CI 0.92 to 4.61) for ESDI >25 mm/m^2 OR EDD >65 mm vs. ESDI ≤25 mm/m^2 AND EDD ≤65 mm** There were 31 late deaths during follow-up. Overall survival was as follows for the two groups at 5, 10 and 15 years, respectively: • ESDI ≤25 mm/m^2 **AND** EDD ≤65: 95% (86-98%), 86% (71-94%) and 73% (54-86%) • ESDI >25 mm/m^2 **OR** EDD >65: 96% (89-98%), 88% (79-94%) and 64% (49-76%) Analysis 2 – those that survived >10 years post-aortic valve replacement **HR 2.7 (95% CI 0.9 to 10.4) for ESDI >25 mm/m^2 OR EDD >65 mm vs. ESDI ≤25 mm/m^2 AND EDD ≤65 mm** Overall survival at 15 years: • ESDI ≤25 mm/m^2 **AND** EDD ≤65: 85% (62-95%)

Reference	**Maeda 2019[156]**
	• ESDI >25 mm/m^2 **OR** EDD >65: 72% (56-84%)
Comments	**Analysis 1** 1. Study participation LOW 2. Study attrition LOW 3. Prognostic factor measurement HIGH 4. Outcome Measurement HIGH 5. Study confounding LOW 6. Statistical analysis HIGH 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH Potential prognostic factor indirectness: thresholds used to not match those specified in the protocol **Analysis 2** 1. Study participation LOW 2. Study attrition LOW 3. Prognostic factor measurement HIGH 4. Outcome Measurement HIGH 5. Study confounding LOW 6. Statistical analysis HIGH 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH Potential prognostic factor indirectness: thresholds used to not match those specified in the protocol

1

2

Reference	**Pizarro 2011[209]**
Study type and analysis	Prospective cohort study Multivariate logistic regression analysis

Reference	Pizarro 2011[209]
Number of participants and characteristics	N=294 whole cohort (n=160 in derivation cohort and n=134 in validation cohort, further divided into subgroups based on baseline BNP levels) <u>Analysis 1 – within the derivation cohort (subgroup with BNP <130 pg/ml at baseline, n=118)</u> BNP increased to ≥130 pg/ml at 1 year follow-up, n=4 BNP remained <130 pg/ml at 1 year follow-up, n=114 <u>Analysis 2 – within the validation cohort (subgroup with BNP <130 pg/ml at baseline, n=100)</u> BNP increased to ≥130 pg/ml at 1 year follow-up, n=3 BNP remained <130 pg/ml at 1 year follow-up, n=97 <u>Analysis 3 - within the derivation cohort (whole derivation cohort, n=160 – baseline BNP as a categorical variable)</u> End-systolic diameter/body surface area (ESD/BSA) ≥24 mm/m^2, number not reported End-systolic diameter/body surface area (ESD/BSA) <24 mm/m^2, number not reported <u>Analysis 4 - within the derivation cohort (whole derivation cohort, n=160 – baseline BNP as a categorical variable)</u> End-diastolic diameter (EDD) ≥35 mm/m^2, number not reported End-diastolic diameter (EDD) <35 mm/m^2, number not reported <u>Analysis 5 - within the validation cohort (whole validation cohort, n=134 - baseline BNP as a categorical variable)</u> End-systolic diameter/body surface area (ESD/BSA) ≥24 mm/m^2, number not reported End-systolic diameter/body surface area (ESD/BSA) <24 mm/m^2, number not reported **Inclusion criteria:** Chronic, severe asymptomatic aortic regurgitation (effective regurgitant orifice area ≥30 mm^2 and regurgitant volume ≥60 ml/beat); normal left ventricular ejection fraction (>55%) at rest; preserved exercise tolerance [defined by exercise electrocardiogram performed with Bruce protocol and following requirements: functional capacity ≥7 metabolic equivalents without symptoms (angina or dyspnoea) or any of complex ventricular arrhythmia, hypotension or pathological ST segment deviation.

Reference	Pizarro 2011[209]
	Exclusion criteria: Associated valve disease (aortic stenosis with peak gradient ≥20 mm Hg, moderate or severe mitral regurgitation, haemodynamically significant mitral stenosis or significant right-sided organic valve disease); previous valve or coronary surgery; aortic root enlargement (≥40 mm); aortic dissection; ongoing endocarditis; cardiomyopathies; pericardial disease; history of coronary artery disease. **Derivation cohort – values given as BNP <130 vs. BNP ≥130 pg/ml (n=118 vs. n=42)** • **Mean (SD) age**: 51 (9) vs. 56 (10) years • **Sex**: 55 vs. 57% male • **Valve surgery**: prior valve surgery was an exclusion criterion. • **Single vs multiple valve disease**: other moderate-severe valve disease appears to be excluded, but unclear whether any had mild valve disease associated. • **Co-morbid cardiac abnormalities**: o Atrial fibrillation, 4 vs. 7% o Hypertension, 54 vs. 40% • **Median (IQR) left ventricular ejection fraction:** 64 (57-71) vs. 61 (56-65)% • **Median (IQR) end-diastolic volume:** 97 (56-107) vs. 125 (69-143) ml/m^2 • **Median (IQR) end-systolic volume:** 27 (17-34) vs. 35 (24-40) ml/m^2 • **Median (IQR) end-diastolic diameter/body surface area**: 30 (27-36) vs. 42 (28-47) mm/m^2 • **Median (IQR) end-systolic diameter/body surface area**: 16 (12-21) vs. 26 (18-30) mm/m^2 • **Median (IQR) atrial volume/body surface area**: 57 (37-68) vs. 65 (48-75) cm^3/m^2 • **Median (IQR) pulmonary artery systolic pressure**: 25 (18-31) vs. 33 (22-40) cm^3/m^2 • **Type of aortic regurgitation:** values are for whole cohort o Degenerative, 45% o Congenital (bicuspid), 37.5% o Rheumatic, 7.5% o Post-endocarditis, 6.25% o Miscellaneous, 3.75% • **Medical treatment during study:** o Angiotensin-converting enzyme inhibitor, 57 vs. 50% o Angiotensin II receptor blocker, 23 vs. 26%

Reference	Pizarro 2011[209]
	○ Calcium channel blocker, 16 vs. 17% ○ Aldosterone antagonists, 4.2 vs. 4.7% ○ Beta-blockers, 5 vs. 4.7% ○ Digoxin, 2.5 vs. 2.4% **Validation cohort – values given as BNP <130 vs. BNP ≥130 pg/ml (n=100 vs. n=34)** • **Mean (SD) age**: 52 (9) vs. 57 (8) years • **Sex**: 54 vs. 52% male • **Valve surgery**: • **Single vs multiple valve disease**: • **Co-morbid cardiac abnormalities**: ○ Atrial fibrillation, 4 vs. 6% ○ Hypertension, 55 vs. 42% • **Median (IQR) left ventricular ejection fraction:** 65 (58-79) vs. 62 (57-65)% • **Median (IQR) end-diastolic volume:** 95 (55-105) vs. 119 (61-136) ml/m^2 • **Median (IQR) end-systolic volume:** 25 (18-32) vs. 34 (22-39) ml/m^2 • **Median (IQR) end-diastolic diameter/body surface area**: 32 (28-37) vs. 40 (31-45) mm/m^2 • **Median (IQR) end-systolic diameter/body surface area**: 15 (13-22) vs. 24 (20-27) mm/m^2 • **Median (IQR) atrial volume/body surface area**: 54 (34-62) vs. 63 (39-79) cm^3/m^2 • **Median (IQR) pulmonary artery systolic pressure**: 23 (15-29) vs. 34 (21-42) cm^3/m^2 • **Type of aortic regurgitation:** values are for whole cohort ○ Degenerative, 48.5% ○ Congenital (bicuspid), 38.1% ○ Rheumatic, 6.7% ○ Post-endocarditis, 4.5% ○ Miscellaneous, 2.2% • **Medical treatment during study:** ○ Angiotensin-converting enzyme inhibitor, 50 vs. 47% ○ Angiotensin II receptor blocker, 23 vs. 20% ○ Calcium channel blocker, 16 vs. 18% ○ Aldosterone antagonists, 4 vs. 3%

Reference	Pizarro 2011[209]
	○ Beta-blockers, 3 vs. 3% ○ Digoxin, 2 vs. 3% **Population source:** consecutive patients from single centre.
Prognostic variable	**In those that were treated conservatively initially:** Patients censored from the analysis when they died or underwent surgery, suggesting initial strategy was conservative. Decisions about valve surgery were left to treating physicians. <u>Analysis 1 – within the derivation cohort (subgroup with BNP <130 pg/ml at baseline, n=118)</u> BNP increased to ≥130 pg/ml at 1 year follow-up BNP remained <130 pg/ml at 1 year follow-up (referent) <u>Analysis 2 – within the validation cohort (subgroup with BNP <130 pg/ml at baseline, n=100)</u> BNP increased to ≥130 pg/ml at 1 year follow-up BNP remained <130 pg/ml at 1 year follow-up (referent) <u>Analysis 3 - within the derivation cohort (whole derivation cohort, n=160 – baseline BNP as a categorical variable)</u> End-systolic diameter/body surface area (ESD/BSA) ≥24 mm/m^2 End-systolic diameter/body surface area (ESD/BSA) <24 mm/m^2 (referent) <u>Analysis 4 - within the derivation cohort (whole derivation cohort, n=160 – baseline BNP as a categorical variable)</u> End-diastolic diameter (EDD) ≥35 mm/m^2 End-diastolic diameter (EDD) <35 mm/m^2 (referent) <u>Analysis 5 - within the validation cohort (whole validation cohort, n=134 - baseline BNP as a categorical variable)</u> End-systolic diameter/body surface area (ESD/BSA) ≥24 mm/m^2 End-systolic diameter/body surface area (ESD/BSA) <24 mm/m^2 (referent) Mean (SD) follow-up was 46 (10) months in the derivation cohort and 38 (9) months in the validation cohort. Follow-up was complete in all but 3 patients – n=2 missing from derivation cohort and n=1 missing from validation cohort.
Confounders	Multivariate regression models incorporated clinical and echocardiographic variables that were demonstrated to be associated with the end-point on univariate analysis: BNP (different analyses using it as a continuous and categorical variable), ESD/BSA, EDD/BSA, effective regurgitant orifice area, atrial volume indexed by BSA, age, pulmonary artery systolic pressures, left ventricular ejection

Reference	Pizarro 2011[209]
	fraction and left ventricular volumes. Unclear whether the factors adjusted for may have different or analyses 1 and 2 where a different subgroup was used, but this is not stated.
Outcomes and effect sizes	**Appearance of either congestive heart failure of left ventricular dysfunction, or left ventricular systolic dysfunction symptoms or death** Analysis 1 – within the derivation cohort (subgroup with BNP <130 pg/ml at baseline, n=118) **HR 7.6 (95% CI 4.2 to 19.6) for BNP increase to ≥130 pg/ml vs. BNP retained <130 pg/ml at 1 year** N=4 developed BNP level ≥130 pg/ml at 1 year who had a level below this at baseline and all of these experienced the outcome at follow-up. Analysis 2 – within the validation cohort (subgroup with BNP <130 pg/ml at baseline, n=100) **HR 8.6 (95% CI 3.5 to 19.8) for BNP increase to ≥130 pg/ml vs. BNP retained <130 pg/ml at 1 year** N=3 developed BNP level ≥130 pg/ml at 1 year who had a level below this at baseline and all of these experienced the outcome at follow-up. Analysis 3 - within the derivation cohort (whole derivation cohort, n=160 – baseline BNP as a categorical variable) **OR 3.4 (95% CI 1.88 to 11.9) for ESD/BSA ≥24 mm/m^2 vs. ESD/BSA <24 mm/m^2** N=45 experienced left ventricular systolic dysfunction symptoms or death. There were n=3 deaths (sudden in 2 patients and due to congestive heart failure in 1 patient). Additionally, n=29 developed congestive heart failure and n=15 developed left ventricular dysfunction. Aortic valve surgery was performed in 50 (31%) patients during follow-up. Analysis 4 - within the derivation cohort (whole derivation cohort, n=160 – baseline BNP as a categorical variable) **OR 2.1 (95% CI 0.88 to 13.7) for EDD ≥35 mm/m^2 vs. EDD <35 mm/m^2** N=45 experienced left ventricular systolic dysfunction symptoms or death. There were n=3 deaths (sudden in 2 patients and due to congestive heart failure in 1 patient). Additionally, n=29 developed congestive heart failure and n=15 developed left ventricular dysfunction. Aortic valve surgery was performed in 50 (31%) patients during follow-up. Analysis 5 - within the validation cohort (whole validation cohort, n=134 - baseline BNP as a categorical variable) **OR 3.4 (95% CI 1.7 to 14.7) for ESD/BSA ≥24 mm/m^2 vs. ESD/BSA <24 mm/m^2**

Reference	Pizarro 2011[209]
	N=35 experienced left ventricular systolic dysfunction symptoms or death. There were n=2 deaths (sudden in 1 patient and non-cardiac-related in 1 patient). In addition, n=26 patients developed congestive heart failure and n=14 patients developed left ventricular dysfunction. Aortic valve surgery was performed in 39 (29.1%) patients.
Comments	**Analysis 1** 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 Potential outcome indirectness: composite outcome of various different end-points **Analysis 2** 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 Potential outcome indirectness: composite outcome of various different end-points **Analysis 3** 1. Study participation HIGH

Reference	Pizarro 2011[209]	
	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
	Potential prognostic factor indirectness: threshold different to that specified in protocol Potential outcome indirectness: composite outcome of various different end-points	
	Analysis 4	
	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
	Potential prognostic factor indirectness: threshold different to that specified in protocol Potential outcome indirectness: composite outcome of various different end-points	
	Analysis 5	
	1. Study participation	HIGH
	2. Study attrition	LOW
	3. Prognostic factor measurement	LOW
	4. Outcome Measurement	HIGH
	5. Study confounding	HIGH

Reference	Pizarro 2011[209]	
	6. Statistical analysis	HIGH
	7. Other risk of bias	LOW
	OVERALL RISK OF BIAS	VERY HIGH
	Potential prognostic factor indirectness: threshold different to that specified in protocol Potential outcome indirectness: composite outcome of various different end-points	

1

D.3 Mitral regurgitation

Reference	Arias 2013[6]
Study type and analysis	Prospective single-centre cohort study Multivariate logistic regression model
Number of participants and characteristics	N=144 Left atrial volume index ≥55 ml/m^2 n=48 Left atrial volume index <55 ml/m^2, n=96 **Inclusion criteria:** Asymptomatic patients aged > 18 years with diagnoses by echocardiography of at least moderate MR (effective regurgitant orifice area [EROA] ≥0.20 cm^2) with adequate follow-up and an organic cause of regurgitation. **Exclusion criteria:** Symptoms of heart failure (New York Heart Association functional class ≥II), left ventricular systolic dysfunction (LVEF < 60% and/or ESD > 40 mm), atrial fibrillation, concomitant valve disorders (moderate or severe aortic disease, moderate or severe mitral stenosis, or significant right-sided organic, valve disease), ischemic MR, prior valve or coronary surgery, cardiomyopathies and pericardial diseases, congenital heart disease, end-stage disease with survival < 1 year, or a poor echocardiographic window. • **Mean (SD) age**: 71 (12) years • **Sex**: 44% male

Reference	Arias 2013[6]

	• **Mitral valve surgery**: 18%
	• **Single vs multiple valve disease**: concomitant valve disorders excluded
	• **Co-morbid cardiac abnormalities**:
	  ○ Hypertension, 4.9%
	• **Etiology**:
	  ○ Degenerative, 88.9%
	  ○ Rheumatic, 3.5%
	  ○ Post-endocarditis, 2.1%
	  ○ Fibrosis, 5.6%
	• **Echo variables, mean (SD)**
	  ○ LVEF: 66 (4.8)%
	  ○ End diastolic volume: 87 (34) ml
	  ○ **end-diastolic diameter:** 5.23 (0.59) cm
	  ○ **end-systolic diameter:** 3.03 (0.53) cm
	• **Regurgitant volume, mean (SD):** 74 (27) ml
	• **EROA, mean (SD):** 0.47 (0.11) cm^2
	• **EROA ≥0.40 cm^2** (BSE classification for severe MR): 72.9%
	• **Left atrial volume, mean (SD):** 86 (34) ml
	
	Population source: unclear source and recruitment period.
	Median follow-up 2.76 years (interquartile range, 1.86–3.48 years).
	
	Echocardiographic readings were averaged by two independent observers, who were blinded to the clinical information.

Prognostic variables	Left atrial volume index ≥55 ml/m^2 Left atrial volume index <55 ml/m^2 (referent) Median follow-up was 2.76 years across the cohort.
Confounders	EROA ≥0.55 cm2 and deceleration time ≤160 msec Note that results only given for those that were significant on multivariate analysis.
Outcomes and effect sizes	**Development of symptoms and/or LV dysfunction during follow-up.**

Reference	Arias 2013[6]
	The presence of symptoms during follow-up was defined as the occurrence of NYHA functional class II to IV dyspnea. The presence of LV dysfunction was defined as LVEF < 60% during follow-up. **Adjusted OR 2.26 (95% CI 1.04 to 4.88) for** LAVI ≥55 ml/m^2 vs LAVI < 55 mL/m^2 During median 2.76-year follow-up, among the whole cohort, 54 of 144 patients (37.50%) reached the combined end point. Twelve of 144 patients (8.33%) died; seven of these deaths (58%) were cardiovascular in origin. Fifty-two of 144 patients had dyspnoea (36.11%), and 10 of 144 patients (6.94%) had ventricular dysfunction. Patients with basal LAVI ≥55 ml/m^2 vs those with LAVI < 55 mL/m^2, had higher mortality (16.66% vs 4.16%, P = .010), higher incidence of dyspnoea (52.08% vs 28.12%, P = .004), and greater need for mitral valve surgery (37.5% vs 8.33%, P = .000). There was no significant difference in ventricular dysfunction (6.25% vs 7.29, P = .816). The combined end point rate was higher in patients with basal LAVI ≥55 ml/m^2 than in those with LAVI <55 ml/m^2 (54.16% vs 29.16%; Mitral valve surgery was performed in 26 of 144 patients (18.06%). Eighteen of 144 patients (12.50%) developed atrial fibrillation. Events were collected by an investigator who was blinded to the clinical and echocardiographic data. 1 patient lost to follow-up.
Comments and 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 Potential population indirectness: Authors note that patients classified as asymptomatic or mildly symptomatic on basis of NYHA classification and not exercise testing. Prognostic factor indirectness: LAVI threshold does not match protocol

Reference	Chenot 2009[51]
Study type and analysis	Retrospective cohort study of those in a single institution admitted between 1st January 1990 and 31st December 2001 with asymptomatic severe degenerative mitral regurgitation undergoing mitral valve repair. Multivariate Cox proportional hazards model

Number of participants and characteristics	N=143
	
	LVEF <60%, number not reported
	LVEF ≥60%, number not reported
	
	Inclusion criteria:
	Severe (grade 3), degenerative mitral regurgitation that received mitral valve repair between 1st January 1990 and 31st December 2001. Patients who had coronary artery disease or had undergone coronary artery bypass grafting were not excluded.
	
	Exclusion criteria:
	Age >85 years; associated mitral stenosis; previous valve surgery; and associated congenital heart disease.
	
	• **Mean (SD) age**: 63.29 (12.87) years
	• **Sex**: 74% male
	• **Valve surgery**: all underwent mitral valve repair as part of the inclusion criteria of study. In addition, 22.4% underwent concomitant coronary artery bypass grafting.
	• **Single vs multiple valve disease**: proportion with other types of valve disease unclear. Associated mitral stenosis was an exclusion criterion.
	• **Co-morbid cardiac abnormalities**:
	  ○ Hypertension, 33.2%
	• **Prolapse type**:
	  ○ Posterior, 69.9%
	  ○ Anterior, 11.9%
	  ○ Bileaflet, 17.9%
	• **Systolic tricuspid gradient >40 mmHg**, 14.6%
	• **Mean (SD) left ventricular ejection fraction:** 67.24 (8.65)%

Reference	Chenot 2009[51]
	• **Mean (SD) left ventricular end-diastolic diameter:** 59.64 (7.81) mm • **Mean (SD) left ventricular end-systolic diameter:** 37.01 (5.66) mm • **Mean (SD) left atrial size:** 49.68 (9.17) mm Population source: consecutive patients from single institution between January 1990 and December 2001. Prospectively entered into database but retrospectively reviewed for this study.
Prognostic variables	**In those that received mitral valve repair:** LVEF <60% LVEF ≥60% (referent) Median follow-up was 8 years across the cohort. Information on postoperative events was obtained for all patients between December 2006 and April 2007.
Confounders	Age and diabetes mellitus potentially included in the multivariate model for cardiac mortality alongside LVEF <60%, however this is slightly unclear as no multivariable estimate provided for diabetes mellitus. Note that results only given for those that were significant on multivariate analysis.
Outcomes and effect sizes	**Cardiac mortality** **HR 3.9 (95% CI 1.1 to 13.7) for LVEF <60% vs. LVEF ≥60%** During median 8-year follow-up, 21 patients died, with cardiac causes of death in 13 of these patients (n=3 operative deaths, n=3 due to intractable heart failure, n=5 sudden cardiac death, n=1 thromboembolic stroke and n=1 due to abdominal aortic aneurysm rupture). 30-day mortality was 2%. At 10 years, overall survival was 82±4% and cardiovascular survival was 90±3%.
Comments and 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

Reference	Chenot 2009[51]
	Potential population indirectness: Authors note that patients classified as asymptomatic or mildly symptomatic on basis of NYHA classification and not exercise testing, as exercise testing results were not available in a large majority of the patients based on retrospective design of the study.

1

Reference	Coutinho 2014[59]
Study type and analysis	Retrospective cohort study, reviewing patients admitted between January 1992 and December 2012. Multivariable Cox proportional hazards model.
Number of participants and characteristics	N=382 <u>Analysis 1</u> Presence of atrial fibrillation OR pulmonary hypertension, n=106 Absence of atrial fibrillation AND pulmonary hypertension, n=276 <u>Analysis 2</u> P2 prolapse present, n=268 P2 prolapse not present, n=114 <u>Analysis 3</u> Myxomatous valves, n=272 Non-myxomatous valves, n=110 **Inclusion criteria:** Severe pure or predominant mitral regurgitation that underwent mitral valve surgery; asymptomatic or mildly symptomatic (New York Heart Association class I or II); severe degenerative mitral regurgitation (3+); preserved left ventricular function. **Exclusion criteria:** Patients that underwent additional procedures other than isolated mitral surgery with or without concomitant tricuspid valve annuloplasty; New York Heart Association class III or IV; left ventricular ejection fraction <60%; left ventricular end-systolic internal diameter ≥45 mm; coronary artery disease; aortic valve disease; hypertrophic cardiomyopathy; ascending aortic aneurysms; previous mitral valve surgery.

Reference	Coutinho 2014[59]
	• **Mean (SD) age**: 55.7 (14.2) years • **Sex**: 73% male • **Valve surgery**: all received mitral valve intervention as treatment strategy. The following received each type of operation: o Mitral valve repair, 98.2% - Ring annuloplasty, 95.3% - Leaflet resection, 70.9% - Artificial chordae: anterior leaflet, 28.5% and posterior leaflet, 7.9% - Chordal transfer/shortening, 7.4% - Commissural closure, 8.6% - Papillary muscle shortening, 5.2% - Tricuspid annuloplasty, 7.9% o Mitral valve replacement, 1.8% (this was 3.4% during the study period) • **Single vs multiple valve disease**: aortic valve disease was an exclusion criterion. Unclear if any concomitant mitral stenosis. Tricuspid regurgitation reported in a proportion of patients: o Tricuspid regurgitation (>2+), 9.7% • **Co-morbid cardiac abnormalities**: o Hypertension, 27.7% o Atrial fibrillation, 16.8% o Pulmonary hypertension OR atrial fibrillation, 24.4% • **Previous stroke**: 3.4% • **Type of mitral valve pathology**: o Myxomatous, 71.2% o Severe myxomatous involvement (Barlow's disease), 17.0% o Isolated posterior prolapse, 55.2% o Isolated anterior prolapse, 13.1% o Bileaflet prolapse, 26.7% o Segment P2 involvement, 70.2% o Segment A2 involvement, 27.7% o Chordal rupture, 55.0% o Isolated annular dilatation, 3.7%

Reference	Coutinho 2014[59]
	○ Fibroelastic deficiency, 25.1% • New York Heart Association class: ○ Class I, 71.2% ○ Class II, 28.8% • **Mean (SD) ejection fraction**: 69.8 (7.5)% • **Mean (SD) left ventricular systolic diameter**: 37.2 (4.2) mm • **Mean (SD) left ventricular diastolic diameter**: 62.0 (6.6) mm • **Mean (SD) left atrium diameter**: 50.8 (8.5) mm Population source: consecutive patients undergoing surgery between January 1992 and December 2012. Appears to be single centre but not explicitly stated.
Prognostic variable	**In those that were treated surgically**: all underwent isolated mitral valve surgery with or without concomitant tricuspid valve annuloplasty for functional regurgitation. Repair was oriented to correct all lesions causing mitral dysfunction following the classic Carpentier principles. <u>Analysis 1</u> Presence of atrial fibrillation OR pulmonary hypertension Absence of atrial fibrillation AND pulmonary hypertension (referent) <u>Analysis 2</u> P2 prolapse present P2 prolapse not present (referent) <u>Analysis 3</u> Myxomatous valves Non-myxomatous valves (referent) Mean (SD) follow-up for the entire cohort was 8.6 (7.5) years (range, 0.6-21.9) years. Cumulative follow-up for entire cohort was 3732 patient-years. Follow-up was complete for 98% of patients.
Confounders	The following factors were included in the multivariate analyses:

Reference	Coutinho 2014[59]
	• Mortality (late mortality): age, chronic obstructive pulmonary disease and presence of atrial fibrillation or pulmonary hypertension. Others are listed and may have been included but this is unclear as no multivariate results given for them in the table (myxomatous valves, tricuspid regurgitation ≥2+, left atrium dimension and P2 prolapse). • Mitral reoperation: myxomatous valves, presence of atrial fibrillation or pulmonary hypertension, P2 prolapse and chordal shortening. Others are listed and may have been included but this is unclear as no multivariate results given for them in the table (diabetes, anterior leaflet prolapse, posterior leaflet prolapse and posterior leaflet resection). Atrial fibrillation and pulmonary hypertension (or systolic pulmonary artery pressure) were not included separately in the multivariate analysis to avoid multicollinearity with the composite outcome. Criteria for entry and retention in the multivariable models were set at 0.1 and 0.05 confidence levels, respectively.
Outcomes and effect sizes	**Mortality (late mortality)**: no clear definition of what 'late' mortality refers to. 30-day mortality was 0.8% (3 patients, n=1 cerebrovascular accident and n=2 cardiac deaths). Overall survival at 5, 10, 15 and 20 years was 96.3±1.0%, 89.7±2.0%, 83.3±3.0% and 72.4±5.8%, respectively. <u>Analysis 1 – AF/PHT</u> **HR 2.54 (95% CI 1.17 to 4.80) for presence of AF or PHT vs. absence of AF and PHT** Long-term survival at 5, 10 and 20 years was as follows for the two groups: • 88.8±3.4%, 75.9±5.8% and 34.1±24.4%, respectively, for patients with AF/PHT • 99.0±1.0%, 97.5±1.8% and 55.7±16.9%, respectively, for patients without AF/PHT **Mitral reoperation**: There were 2 early (in-hospital) failures of mitral valve repair – both were re-repaired and preserved. N=10 patients required mitral valve operation for significant mitral regurgitation late after the initial procedure. The mean (SD) time from first surgery to reoperation was 8.6 (5.1) years. The valve was replaced in n=8 cases. Freedom from mitral valve reoperation at 1, 10 and 20 years was 99.7±0.3%, 96.5±1.4% and 93.1±2.4%, respectively. <u>Analysis 1 – AF/PHT</u> **HR 4.20 (95% CI 1.10-11.20) for presence of AF or PHT vs. absence of AF and PHT** Survival free from mitral reoperation at 20 years was 86.3±6.9% for those with AF/PHT vs. 93.7±3.0% for those without AF/PHT.

Reference	Coutinho 2014[59]
	Analysis 2 – P2 prolapse **HR 0.06 (95% CI 0.01 to 0.51) for P2 prolapse present vs. P2 prolapse not present** Analysis 3 – myxomatous valves **HR 0.07 (95% CI 0.01 to 0.62) for myxomatous valves vs. non-myxomatous valves**
Comments	**Mortality – analysis 1** 1. Study participation HIGH 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement HIGH 5. Study confounding HIGH 6. Statistical analysis VERY HIGH 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH Potential population indirectness: some (28%) included that are minimally symptomatic (NYHA class II) rather than asymptomatic Potential prognostic factor indirectness: composite prognostic factor of atrial fibrillation or pulmonary hypertension, rather than atrial fibrillation which is pre-specified in protocol **Mitral reoperation – analysis 1** 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 Potential population indirectness: some (28%) included that are minimally symptomatic (NYHA class II) rather than asymptomatic

Reference	Coutinho 2014[59]
	Potential prognostic factor indirectness: composite prognostic factor of atrial fibrillation or pulmonary hypertension, rather than atrial fibrillation which is pre-specified in protocol Potential outcome indirectness: indirect outcome compared with protocol but may partially cover the heart failure hospitalisation outcome **Mitral reoperation – analysis 2** 1. Study participation HIGH 2. Study attrition LOW 3. Prognostic factor measurement HIGH 4. Outcome Measurement HIGH 5. Study confounding HIGH 6. Statistical analysis HIGH 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH Potential population indirectness: some (28%) included that are minimally symptomatic (NYHA class II) rather than asymptomatic Potential prognostic factor indirectness: specifically P2 prolapse as factor rather than posterior prolapse as a whole as prognostic factor specified in protocol Potential outcome indirectness: indirect outcome compared with protocol but may partially cover the heart failure hospitalisation outcome **Mitral reoperation – analysis 3** 1. Study participation HIGH 2. Study attrition LOW 3. Prognostic factor measurement HIGH 4. Outcome Measurement HIGH 5. Study confounding HIGH 6. Statistical analysis HIGH 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH Potential population indirectness: some (28%) included that are minimally symptomatic (NYHA class II) rather than asymptomatic

Reference	Coutinho 2014[59]
	Potential prognostic factor indirectness: myxomatous valves not listed in protocol as prognostic factor but one component of these valves is said to be ruptured chordae, which is listed in the protocol. Though not all in this group may have had ruptured chordae as part of their valve morphology. Potential outcome indirectness: indirect outcome compared with protocol but may partially cover the heart failure hospitalisation outcome

1

2

Reference	Krauss 2006[135]
Study type and analysis	Prospective cohort study Multivariable Cox proportional hazards regression analysis
Number of participants and characteristics	N=128 <u>Analysis 1</u> Presence of new flail leaflet (NFL), n=30 Absence of new flail leaflet (NFL), n=98 <u>Analysis 2</u> Left ventricular end-systolic diameter (LVESD) >22 mm/m^2, n=23 Left ventricular end-systolic diameter (LVESD) ≤22 mm/m^2, n=105 **Inclusion criteria:** Asymptomatic, organic (non-ischaemic) mitral regurgitation; severe mitral regurgitation (haemodynamically severe based on clinical or echocardiographic evidence or at cardiac catheterisation); ejection fraction >60%. Clinical evaluation supplemented by echocardiography at rest, exercise electrocardiogram or radionuclide cineangiography at rest and during exercise required. **Exclusion criteria:** New York Heart Association class II or worse dyspnoea, angina or fatigue; associated mitral stenosis; mitral regurgitation of ischaemic or myocardiopathic origin; prior mitral valve replacement or repair; and associated pericardial or congenital disease. • **Mean (SD) age**: 60 (8) years

Reference	Krauss 2006[135]

	• **Sex**: 68% male
	• **Valve surgery**: Not reported. Prior mitral valve repair or replacement was an exclusion criterion.
	• **Single vs multiple valve disease**: proportion with other types of valve disease unclear. Associated mitral stenosis was an exclusion criterion.
	• **Co-morbid cardiac abnormalities**:
	  ○ Atrial fibrillation, 12.5%
	• **Cause of valve disease**:
	  ○ Degenerative, 86.7%
	  ○ Rheumatic, 7.8%
	  ○ Endocarditis, 5.5%
	• **Mean (SD) comorbidity index**: 0.84 (0.16)
	• **Mean (SD) left ventricular ejection fraction:** 66 (3)%
	• **Mean (SD) left ventricular end-diastolic diameter:** 34 (5) mm/m^2
	• **Mean (SD) left ventricular end-systolic diameter:** 19 (4) mm/m^2
	• **Mean (SD) left atrial volume:** 116 (40) cm^3
	
	Population source: consecutive patients from single institution. Prospectively enrolled and followed up.

Prognostic variables	**In those treated conservatively:** This is not clear but previous mitral valve intervention was excluded and no mention of any receiving valve intervention as initial treatment strategy. Study states surgery usually performed if symptoms develop or there is a subnormal resting left ventricular function, which was excluded from this study at enrolment, suggesting conservative treatment performed initially. <u>Analysis 1</u> Presence of NFL Absence of NFL (referent) <u>Analysis 2</u> LVESD >22 mm/m^2 LVESD ≤22 mm/m^2 (referent) Mean (SD) follow-up was 34 (14) months (range, 6-66 months).

Reference	Krauss 2006[135]
Confounders	The following factors were included in the multivariate model: new flail leaflet, left ventricular end-systolic diameter >22 mm/m^2, left ventricular end-diastolic diameter >35 mm/m^2, end-systolic diameter >45 mm, regurgitant volume >65 ml/beat, effective regurgitant orifice area >55 mm^2, atrial volume >120 cm^3, E >120 cm/s and pulmonary arterial systolic pressure >35 mmHg. Factors that were significantly associated with the end-point (P<0.10) on univariate analysis were included in the multivariate analysis. A forward stepwise selection method was used to determine the independent end-point predictors. Patients were censored for further analysis when the end-points or death (cardiac or non-cardiac) occurred or when the patient was revascularised and did not present operable symptoms or subnormal ejection fraction during follow-up.
Outcomes and effect sizes	**Occurrence of symptoms and/or left ventricular dysfunction** Analysis 1 **HR 1.6 (95% CI 0.30 to 5.42) for presence of NFL vs. absence of NFL** Analysis 2 **HR 4.5 (95% CI 1.8 to 9.4) for LVESD >22 mm/m^2 vs. LVESD ≤22 mm/m^2** The end-point occurred in 29% of patients during follow-up (37/128) – 25 patients (19.5%) developed symptoms and 17 patients (13.3%) presented with left ventricular dysfunction. Of these, 20 patients (54%) had symptoms and left ventricular dysfunction, 12 patients (32.5%) had symptoms only and 5 patients (13.5%) had left ventricular dysfunction alone. A total of 2 patients (1.5%) died during follow-up and 26 (20.4%) underwent revascularisation. At 5 years, 53±6% remained event-free (asymptomatic with a normal contractile function).
Comments	**Analysis 1** 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

Reference	Krauss 2006[135]
	Potential outcome indirectness: composite outcome of two end-points, one of which is pre-specified in the protocol **Analysis 2** 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 Potential outcome indirectness: composite outcome of two end-points, one of which is pre-specified in the protocol Potential prognostic factor indirectness: different threshold used for the left ventricular end-systolic diameter prognostic factor compared with that listed in the protocol

Reference	Pizarro 2009[208]
Study type and analysis	Prospective single-centre cohort study Multivariate logistic regression and Cox proportional hazards; patients who died or underwent surgery were censored the same day, and those who remained alive were censored at the end of follow-up.
Number of participants and characteristics	N=269 [first consecutive 167 in derivation cohort and next consecutive 102 in validation set] BNP threshold identified in derivation cohort **Derivation cohort** BNP ≥105 pg/ml n=37 BNP ≥105 pg/ml at 1 year in those with baseline <105 pg/ml, n=5 BNP <105 pg/ml, n=130 (referent) BNP remaining <105 pg/ml at 1 year (referent), n=125 **Validation cohort** BNP ≥105 pg/ml n=27 BNP ≥105 pg/ml at 1 year in those with baseline <105 pg/ml, n=4

Reference	Pizarro 2009[208]			
	BNP <105 pg/ml, n=75 (referent)	BNP remaining <105 pg/ml at 1 year (referent), n=71		
	LVESD >22 mm/m^2, n not given in either cohort LVESD ≤22 mm/m^2, n not given in either cohort			
	Inclusion criteria: Severe mitral regurgitation as determined by echocardiographic measurement (effective regurgitant orifice area [EROA]) ≥40 mm2 and regurgitant volume ≥60 ml/beat) and preserved exercise tolerance defined by an exercise electrocardiogram with Bruce protocol and the following requirements: functional capacity ≥7 metabolic equivalents of task (METs) without symptoms or any of the following: complex ventricular arrhythmia, hypotension, or pathological ST-T segment deviation**.** Preserved LVEF >60%. **Exclusion criteria:** associated valve disease (aortic valve disease, moderate or severe mitral stenosis, or significant right organic valve disease), ischemic mitral regurgitation, previous valve or coronary surgery, cardiomyopathies or pericardial diseases, patients with terminal disease whose expected survival was <1 year, patients with poor echocardiographic acoustic window, and those who did not complete the initial exercise test requirements.			
		Derivation set		**Validation set**
		BNP <105	**BNP ≥105 pg/ml**	**BNP <105**	**BNP ≥105 pg/ml**
	• **Mean (SD) age (years)**:	61 (6)	66 (8)	62 (5)	65 (7)
	• **Sex, male (%)**:	59	64	63	65%
	• **Single vs multiple valve disease**: concomitant valve disorders excluded				
	• **Co-morbid cardiac abnormalities**:				
	○ Hypertension (%)	15	21	12	10%
	• **Etiology**:				
	○ Degenerative, 88.9%				
	○ Rheumatic, 3.5%				
	○ Post-endocarditis, 2.1%				
	○ Fibrosis, 5.6%				
	• **Echo variables,** median (IQR)				
	○ LVEF, %:	68 (65-72)	65 (63-68)	68 (65-70)	66 (63-69)
	○ **end-diastolic diameter**, mm/m^2**:**	33 (25-38)	40 (29-46)	32 (24-37)	39 (31-45)
	○ **end-systolic diameter**, mm/m^2**:**	18 (14-23)	24 (19-29)	18 (14-22)	25 (21-30)

Reference	Pizarro 2009[208]				
	• **Regurgitant volume,** ml/beat:	65 (63-70)	76 (66-84)	66 (62-71)	76 (68-86)
	• **EROA, mm²:**	53 (46-61)	65 (47-74)	46 (44-57)	67 (49-81)
	• **Pulmonary artery systolic pressure** (mmHg):	24 (18-30)	32 (24-38)	25 (15-29)	35 (22-39)
	Population source: consecutive patients, recruitment period unclear. Mean follow-up of the derivation set was 36 (8) months. Mean follow-up in the validation set was 31 (9) months. Follow-up was complete in all but 6 cases (4 patients of the derivation set and 2 patients of the validation set). The echocardiographic readings were carried out by 2 independent observers, who were blinded to the clinical and biochemistry information. Decisions about valve surgery were left to the treating physicians, who were unaware of the BNP results. Blood samples were obtained in all patients 24 h after enrollment in the echocardiography laboratory and repeated 1 year later **Derivation set:** Mitral valve surgery was performed in 46 (27.5%) patients. Twenty-seven patients (59%) underwent mitral valve repair, and 19 patients (41%) had mitral valve replacement. Thirty-two patients underwent surgery because of CHF or left ventricular systolic dysfunction. Fourteen patients did not reach the combined end point but underwent surgery, as it was indicated by their referring physician. These patients were not significantly different from patients who reached the combined end point regarding their clinical and echocardiographic variables. BNP in this subset of 14 patients was median 35 pg/ml (IQR 14 to 91 pg/ml). **Validation set:** Mitral valve surgery was performed in 30 patients (29%) of the validation set. Nineteen patients (63%) underwent mitral valve repair and 11 patients (37%) mitral valve replacement. Eleven patients did not reach the combined end point but underwent surgery, as indicated by their referring physician. These patients were not significantly different with regard to clinical and echocardiographic variables from patients who reached the combined end point, and the median BNP value of these 11 patients was 39 (IQR 21 to 93).				
Prognostic variables	Analysis 1 BNP ≥105 pg/ml BNP <105 pg/ml (referent) Analysis 2 BNP ≥105 pg/ml at 1 year in those with baseline <105 pg/ml BNP remaining <105 pg/ml at 1 year (referent) Analysis 3				

Reference	Pizarro 2009[208]
	LVESD >22 mm/m^2, LVESD ≤22 mm/m^2 (referent)
Confounders	Factors associated with the endpoint on univariate analysis (unclear at what threshold of significance so unclear which factors included), assuming variables with p<0.05: age >70 years, LVEF <68%, atrial fibrillation, new flail leaflet, End-diastolic diameter/BSA >35 mm/m2, End-systolic diameter/BSA >22 mm/m2, Regurgitant volume >65 ml/beat, EROA >55 mm2, AV/BSA >70 cm3/m2, Pulmonary artery systolic pressure >35 mm Hg
Outcomes and effect sizes	**Development of congestive heart failure, or LV dysfunction or death during follow-up.** *The presence of CHF was defined as the onset of dyspnoea in NYHA class III to IV, requiring sustained pharmacologic treatment or hospitalisation.* *New onset of left ventricular dysfunction was defined as the assessment of an ejection fraction below 60% during follow-up.* *All outcomes were assessed by 2 investigators blinded to the echocardiographic clinical data. Patients referred for surgery without symptoms or low ejection fraction (decisions regarding surgery left to treating physician) were counted as not reaching an end point in the analysis.* The rate of the combined end point was higher in patients with BNP ≥105 pg/ml than in patients with BNP <105 pg/ml in the derivation set (76% vs. 5.4%) and in the validation set (66% vs. 4%) DERIVATION SET In the derivation set, 35 patients (21%) reached LVDSD. Death occurred in 4 patients (2.4%); it was sudden in 2 patients, due to congestive heart failure in 1 patient, and of noncardiac cause in the remainder. New CHF was diagnosed in 27 patients (17%). Among these 27 patients, 18 received sustained pharmacologic treatment for CHF, and 10 patients required hospitalization for the same reason. Seven patients (4.2%) developed left ventricular dysfunction. Stable NYHA functional class II dyspnoea occurred in 6 patients (3.6%), 7 patients (4.2%) had new-onset atrial fibrillation, and 13 patients (7.8%) developed pulmonary hypertension. **Analysis 1** (using the covariates as categorical variables) **Adjusted OR 4.6 (95% CI 2.7 to 11.6) for** BNP ≥105 pg/ml vs BNP <105 pg/ml **Analysis 2** **Adjusted HR in subset with baseline BNP <105 pg/ml (n= 130) 9.6 (4.9-26.6)** for increase in BNP over 105 pg/ml vs BNP persistent <105 pg/ml *5 (3%) exhibited a BNP elevation above 105 pg/ml at 1 year*

Reference	Pizarro 2009[208]
	Analysis 3 **Adjusted OR 3.4 (95% CI 1.6 to 10.7) for** LVESD/BSA >22 mm/m^2 vs ≤22 mm/m^2 VALIDATION SET In the validation set, 21 patients (20.6%) developed LVDSD. Death occurred in 2 patients (1.96%); it was sudden in 1 patient and noncardiac in another. In addition, 16 patients (15.7%) had CHF (10 patients received sustained pharmacologic treatment for CHF, and 6 patients were hospitalized for the same reason). Finally, 4 patients (3.9%) developed left ventricular dysfunction. Stable NYHA functional class II dyspnea occurred in 4 patients (3.9%), 5 patients (4.9%) experienced new-onset atrial fibrillation, and 10 patients (9.8%) developed pulmonary hypertension during follow-up. **Analysis 1** **Adjusted OR 4.1 (95% CI 2.7 to 12.6) for** BNP ≥105 pg/ml vs BNP <105 pg/ml **Analysis 2** **Adjusted HR in subset with baseline BNP <105 pg/ml (n= 75) 9.6 (3.9-21.1)** for increase in BNP over 105 pg/ml vs BNP persistent <105 pg/ml *4 (5.3%) exhibited a BNP elevation above 105 pg/ml at 1 year* **Analysis 3** **Adjusted OR* 3.1 (95% CI 1.8 to 13.7) for** LVESD/BSA >22 mm/m^2 vs ≤22 mm/m^2 **paper states HR but appears to be in error*
Comments and risk of bias	For all analyses and variables: 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

Reference	Pizarro 2009[208]
	Indirectness: prognostic factor indirectness for analysis 1 and outcome indirectness because a composite is used.

1

2

Reference	Yang 2015[276]
Study type and analysis	Prospective cohort study enrolling between December 2010 and August 2013. Multivariable Cox proportional hazards regression analysis.
Number of participants and characteristics	N=104 Presence of atrial fibrillation (AF), n=20 Absence of atrial fibrillation (AF), n=84 **Inclusion criteria:** Asymptomatic with chronic, severe mitral regurgitation designated as Carpentier type II (mitral valve prolapse or flail, adjudicated by two cardiologists): this included asymptomatic patients without surgical indications as well as asymptomatic patients with class IIA surgical indications (left ventricular end-systolic dimension >40 mm, pulmonary hypertension or atrial fibrillation rhythm) but who refused surgery. **Exclusion criteria:** Left ventricular ejection fraction <60%; mitral regurgitation Carpentier type I or III; caused by regional or global left ventricular remodelling without structural abnormalities of the mitral valve (functional or ischaemic mitral regurgitation); mitral regurgitation caused by rheumatic heart disease; coexistent aortic valve disease; mitral stenosis of more than a mild degree; prior open heart surgery; congenital heart disease; symptoms of heart failure or effort-related limitations in daily activities on the basis of a medical record; prior admission for heart failure; planned mitral valve surgery at time of index echocardiography; inadequate image acquisition. • **Mean (SD) age**: 58.5 (15.1) years • **Sex**: 68% male • **Valve surgery**: those with planned mitral valve surgery at time of index echocardiography were excluded. Those with surgical class IIA indication but who refused surgery, 33%. N=20 (19.2%) had mitral valve intervention during the follow-up.

Reference	Yang 2015[276]

	• **Single vs multiple valve disease**: proportion with other types of valve disease unclear, but any coexistent aortic valve disease and more than mild mitral stenosis were exclusion criteria.
	• **Co-morbid cardiac abnormalities**:
	  ○ Atrial fibrillation, 19%
	  ○ Hypertension, 65%
	• **Flail mitral valve**: 52%
	• **Mean (SD) left ventricular ejection fraction:** 72.7 (7.3)%
	• **Mean (SD) left ventricular end-diastolic volume index:** 60.0 (16.5) ml/m^2
	• **Mean (SD) left ventricular end-systolic volume index:** 16.5 (7.3) ml/m^2
	• **Mean (SD) left ventricular end-systolic dimension index:** 1.98 (0.4) mm/m^2
	• **Mean (SD) left ventricular volume index:** 115.9 (28.9) ml/m^2
	• **Mean (SD) left atrial volume index**: 46.0 (23.1) ml/m^2
	
	Population source: consecutive patients from single institution. Prospectively enrolled and followed up.

Prognostic variable	**In those treated conservatively following initial evaluation:** study included those that had no surgical indications or those with class IIA surgical indications but that refused surgery. Presence of AF Absence of AF (referent) All patients were followed until they either reached the study end-point or reached the end of study follow-up. Mean (SD) follow-up was 13.2 (9.5) months (IQR, 5.0-19.0 months). There was no loss to follow-up as of August 2014.
Confounders	Various different models were used, incorporating different prognostic models in the multivariate analysis or using different forms of the prognostic factors (thresholds or continuous values). <u>Analysis 1</u> Peak positive strain of the left atrium (LASp, continuous), age (continuous), left atrial volume index (LAVi, continuous), left ventricular end-systolic volume index (LVESVi, continuous) and AF were included in the multivariate analysis. <u>Analysis 2</u>

Reference	Yang 2015[276]
	Strain rate in the left atrial conduit phase (LASRr, continuous), age (continuous), LAVi (continuous), LVESVi (continuous) and AF were included in the multivariate analysis. Analyses 1 and 2 were performed separately to avoid collinearity between LASp and LASRr parameters, which are both measures of atrial deformation. Factors with significant correlations (P<0.05) to events were identified to be considered for entering into the multivariate analysis. Other accepted factors affecting atrial deformation with documented importance, regardless of their significance, were also considered for inclusion in the multivariate analysis. All patients were followed until they either reached the study end-point or reached the end of study follow-up.
Outcomes and effect sizes	**Cardiovascular mortality or mitral valve surgery (repair or replacement) caused by new-onset heart failure**: new-onset heart failure was defined as symptom exacerbation requiring hospitalisation with radiographic evidence of pulmonary congestion or heart failure progression identified in the outpatient clinic. Analysis 1 **HR 0.861 (95% CI 0.243 to 3.054) for presence of AF vs. absence of AF** Analysis 2 **HR 0.902 (95% CI 0.253 to 3.216) for presence of AF vs. absence of AF** Overall, 22 patients developed the composite end-point of cardiovascular mortality (n=2 sudden cardiac death, 1 in AF at baseline) or mitral valve surgery (n=20, 4 were in AF rhythm). **Heart failure** Analysis 1 **HR 0.839 (95% CI 0.268 to 2.625) for presence of AF vs. absence of AF** Analysis 2 **HR 0.979 (95% CI 0.302 to 3.167) for presence of AF vs. absence of AF**
Comments	**Cardiovascular mortality or mitral valve surgery (repair or replacement) caused by new-onset heart failure** For both analyses: 1. Study participation HIGH 2. Study attrition LOW

Reference	Yang 2015[276]	
	3. Prognostic factor measurement	HIGH
	4. Outcome Measurement	HIGH
	5. Study confounding	LOW
	6. Statistical analysis	HIGH
	7. Other risk of bias	LOW
	OVERALL RISK OF BIAS	VERY HIGH
	Potential outcome indirectness: composite outcome of two end-points, one of which is pre-specified in protocol	
	Heart failure	
	For both analyses:	
	1. Study participation	HIGH
	2. Study attrition	LOW
	3. Prognostic factor measurement	HIGH
	4. Outcome Measurement	HIGH
	5. Study confounding	LOW
	6. Statistical analysis	HIGH
	7. Other risk of bias	LOW
	OVERALL RISK OF BIAS	VERY HIGH

Appendix E: Forest plots

E.1 Asymptomatic severe aortic stenosis –

E.1.1 Peak aortic jet velocity (Vmax): high versus low

Figure 2: All-cause mortality (fixed effects – comparisons with no heterogeneity)

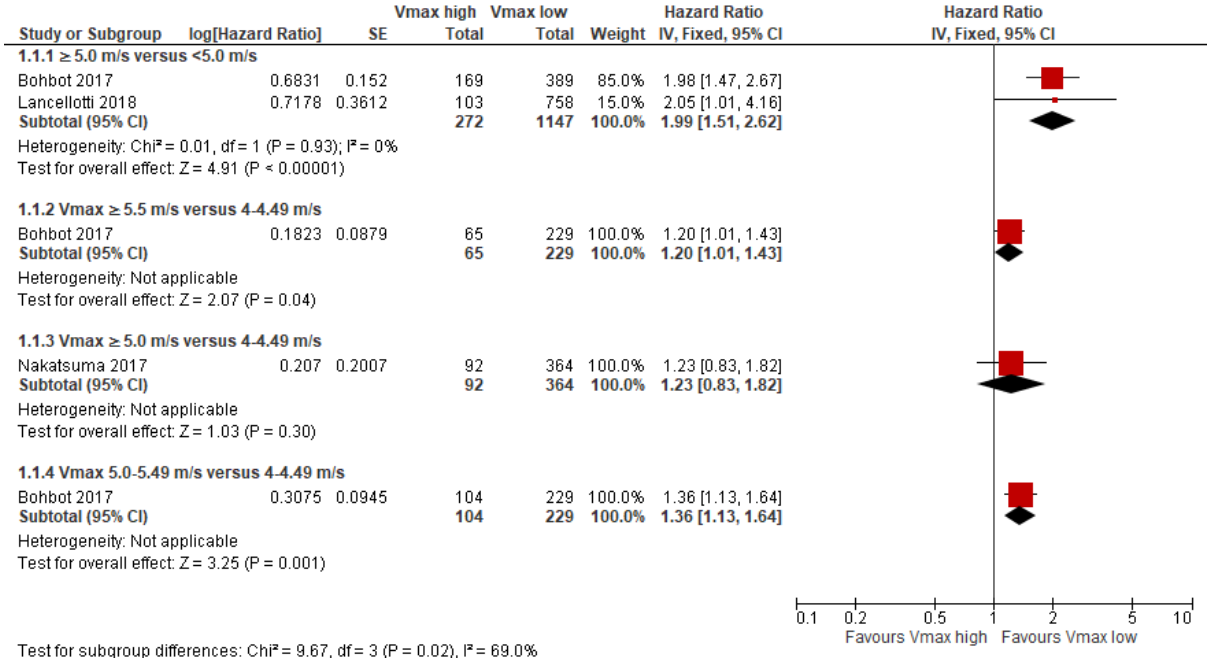


Figure 3: All-cause mortality (random effects – comparison with heterogeneity)

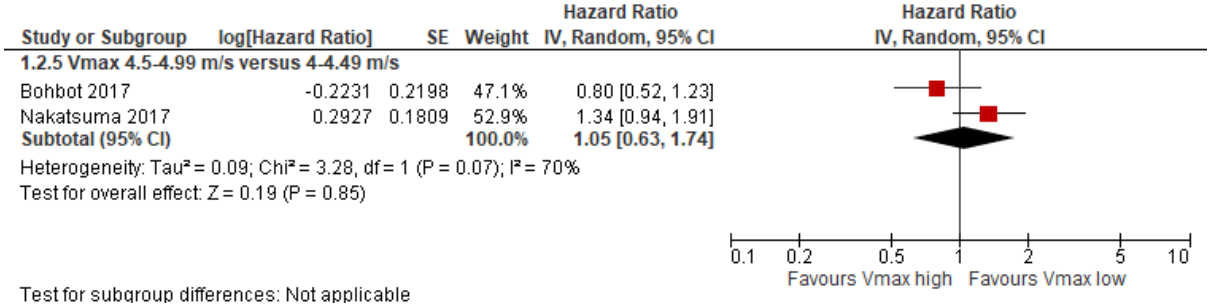
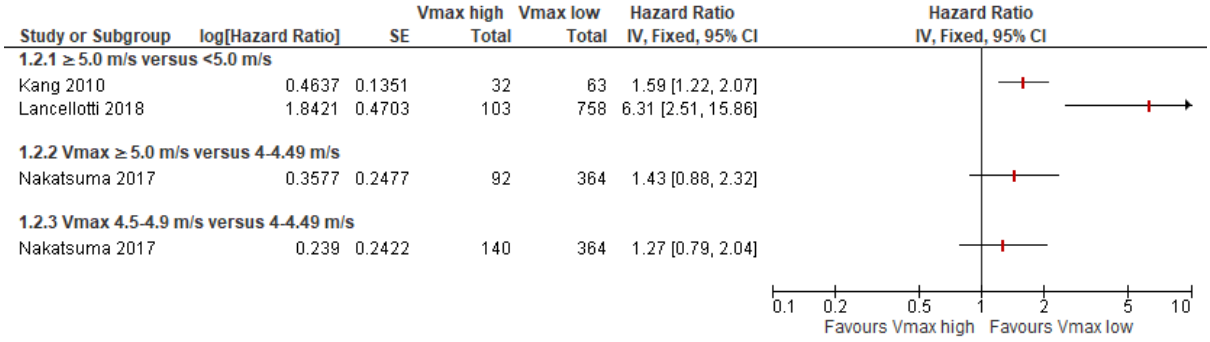
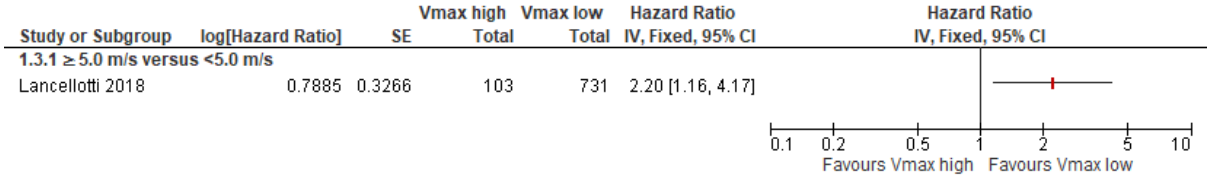


Figure 4: Cardiac or cardiovascular mortality



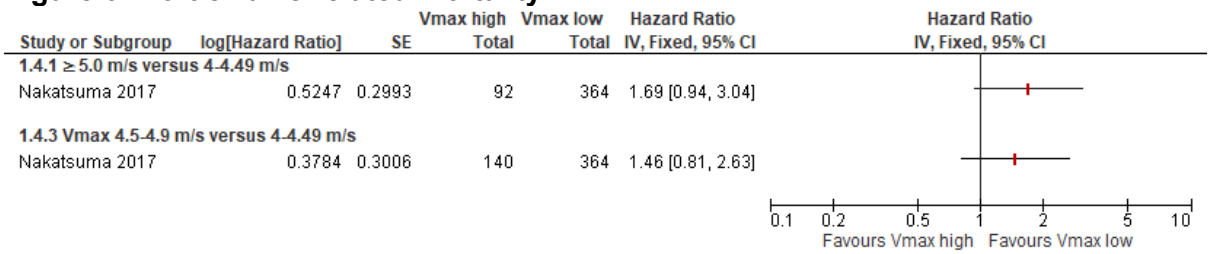
1

Figure 5: Post-AVR mortality (following surgical or transcatheter AVR)



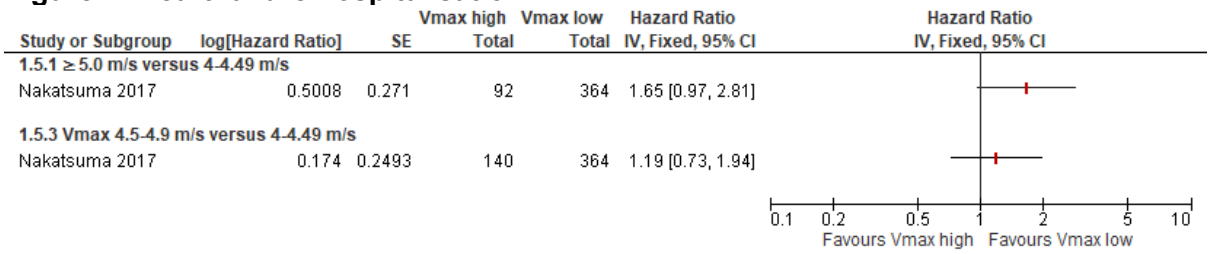
2

Figure 6: Aortic valve-related mortality



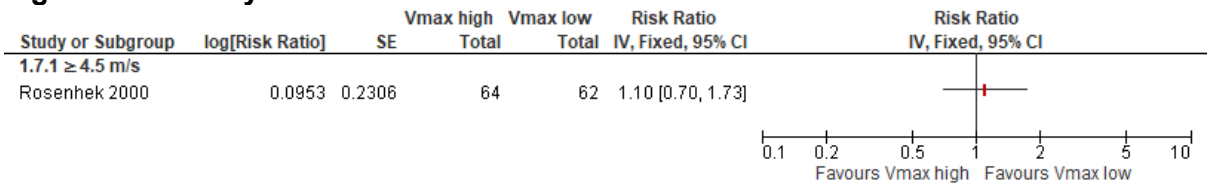
3

Figure 7: Heart failure hospitalisation



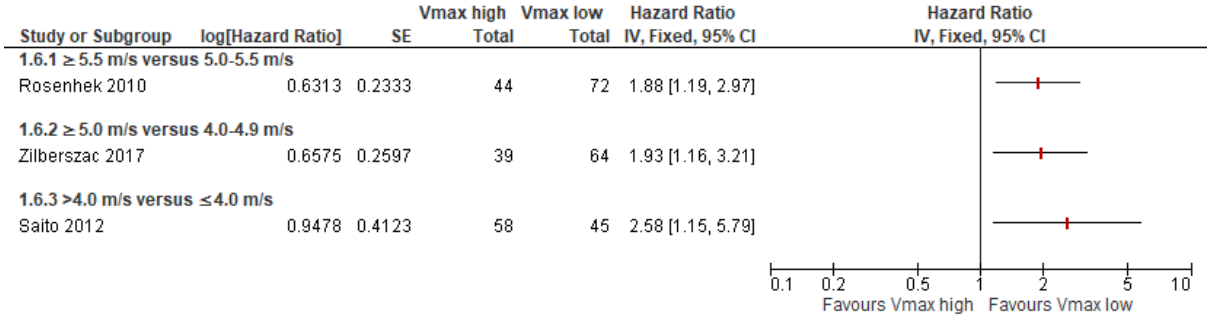
4

Figure 8: Mortality or AVR



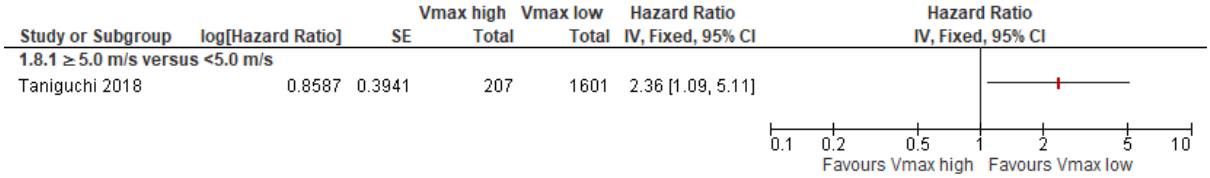
5

Figure 9: Cardiac mortality or AVR indication



1

Figure 10: Sudden death

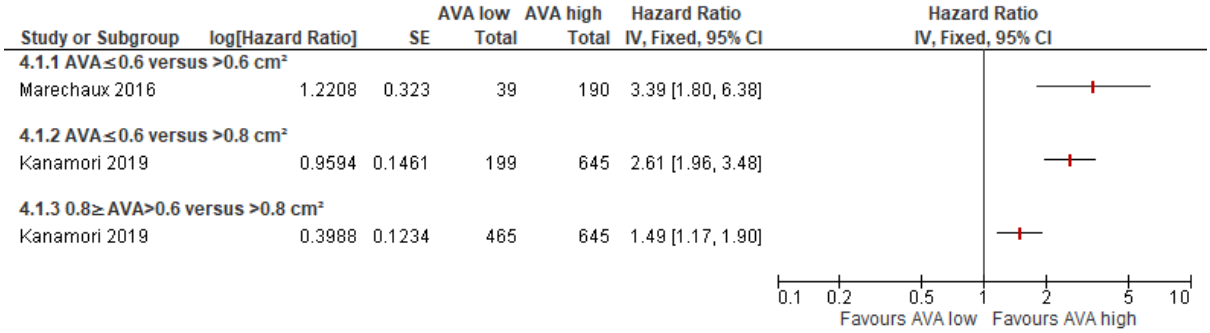


2

E.13.2 Aortic valve area (AVA): low versus high

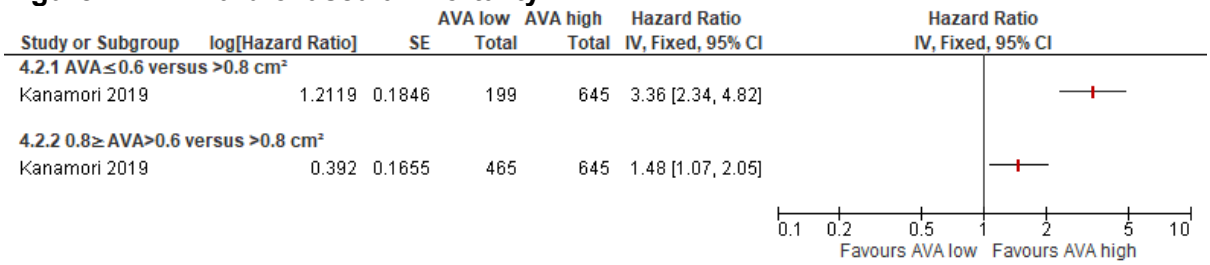
4

Figure 11: All-cause mortality



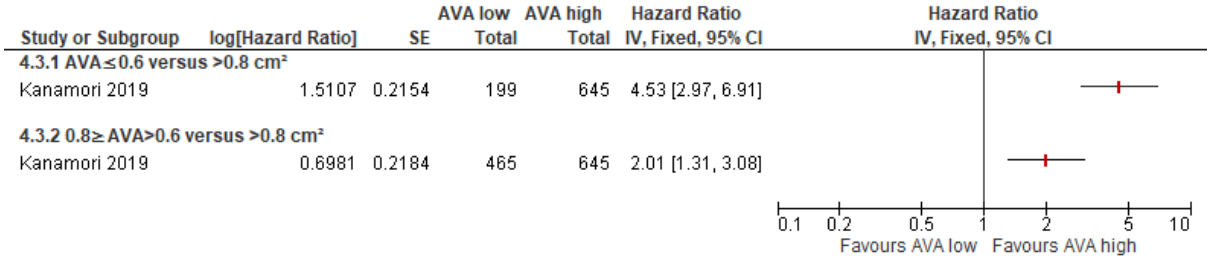
5

Figure 12: Cardiovascular mortality



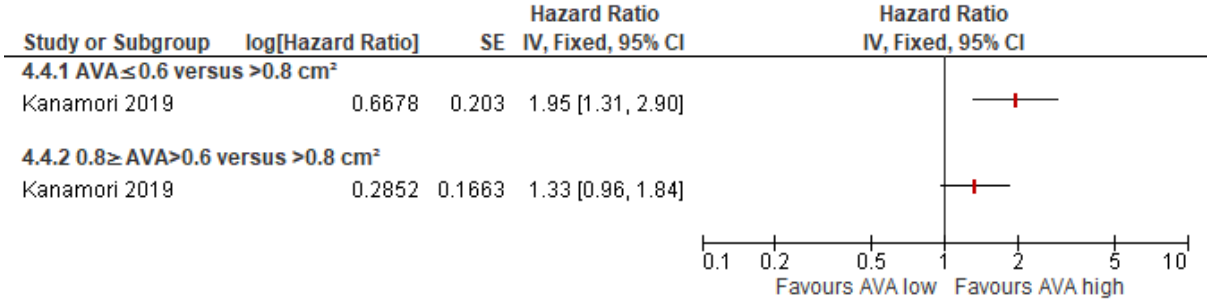
6

Figure 13: Aortic valve-related mortality



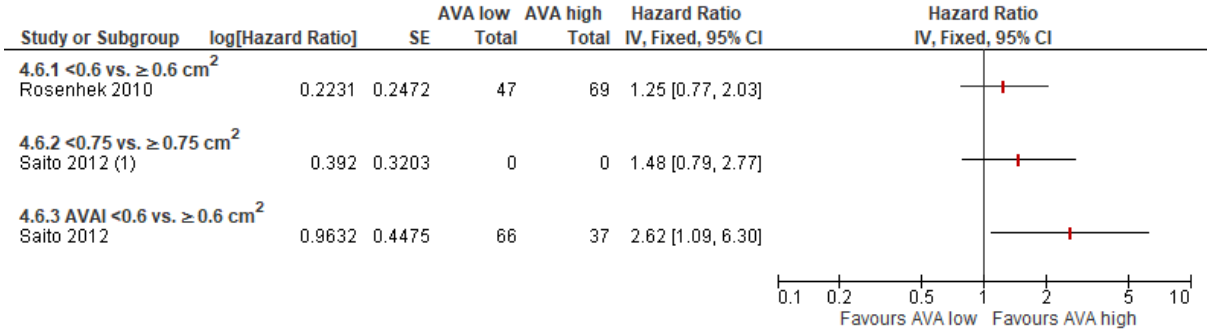
1

Figure 14: Heart failure hospitalisation



2

Figure 15: Cardiac mortality or AVR indication



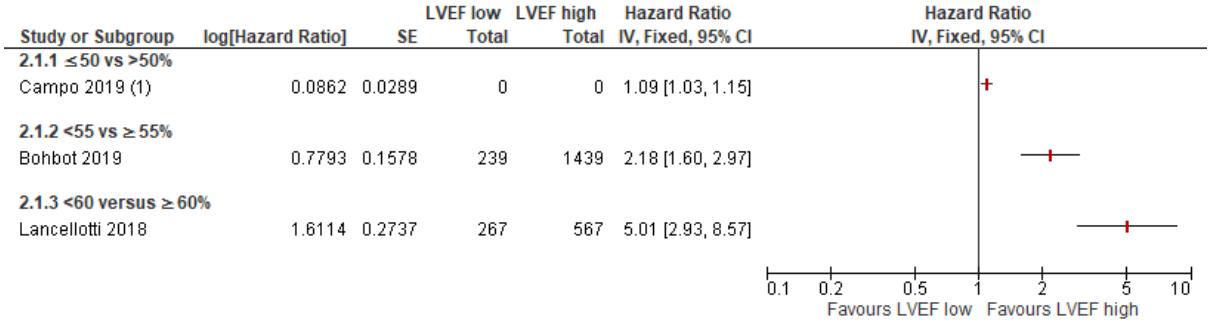
Footnotes
(1) Number for each group not reported

3

E.143 Left ventricular ejection fraction (LVEF): low versus high

5

Figure 16: All-cause mortality



Footnotes
(1) Number in each group not reported

Figure 17: Cardiovascular mortality

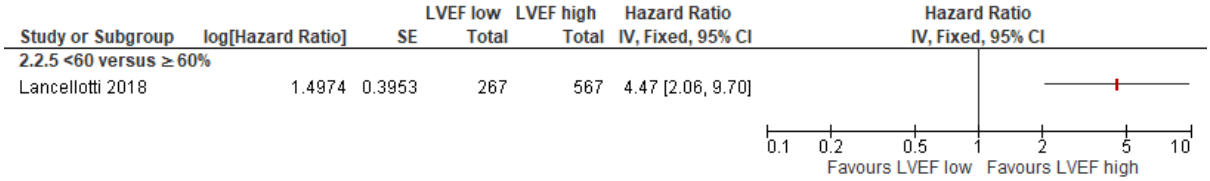


Figure 18: AS-related death or heart failure hospitalisation at 1 year

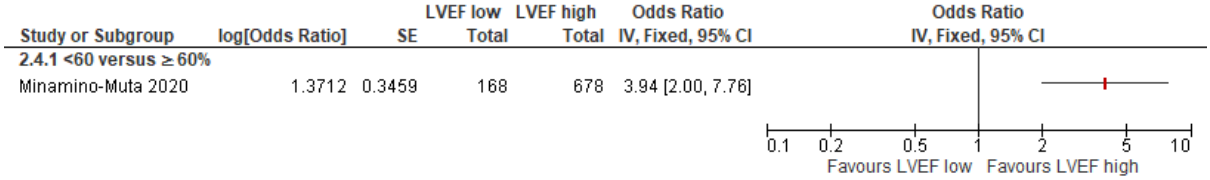
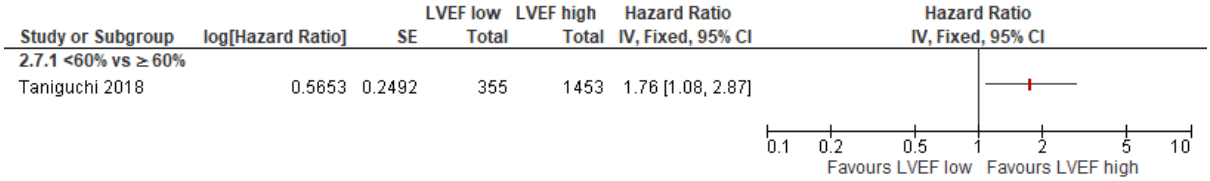
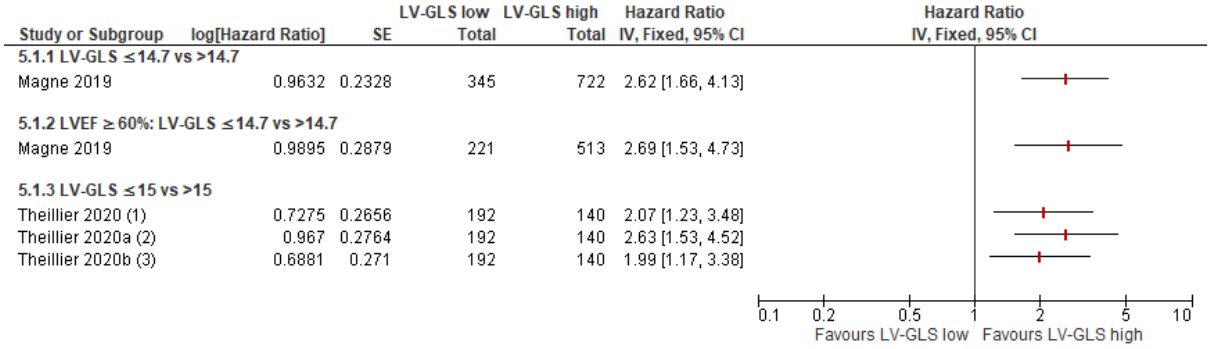


Figure 19: Sudden death



E.154 Left ventricular global longitudinal strain (LV-GLS): low versus high

Figure 20: All-cause mortality



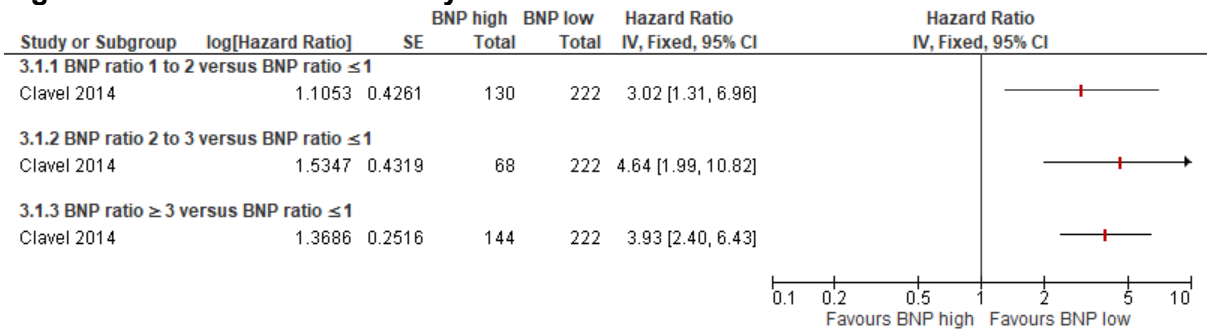
Footnotes
(1) Multivariate model 1
(2) Multivariate model 2
(3) Multivariate model 3

1

E.125 B-type natriuretic peptide (BNP): high versus low

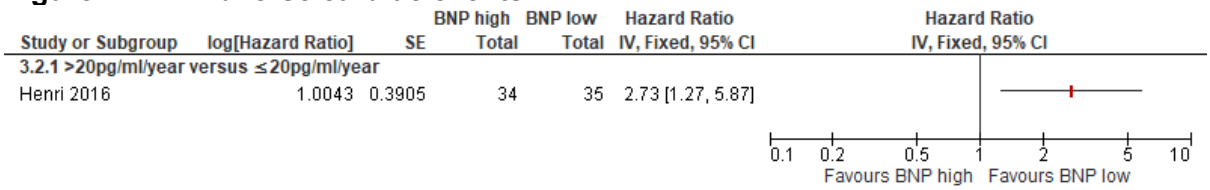
3

Figure 21: All-cause mortality



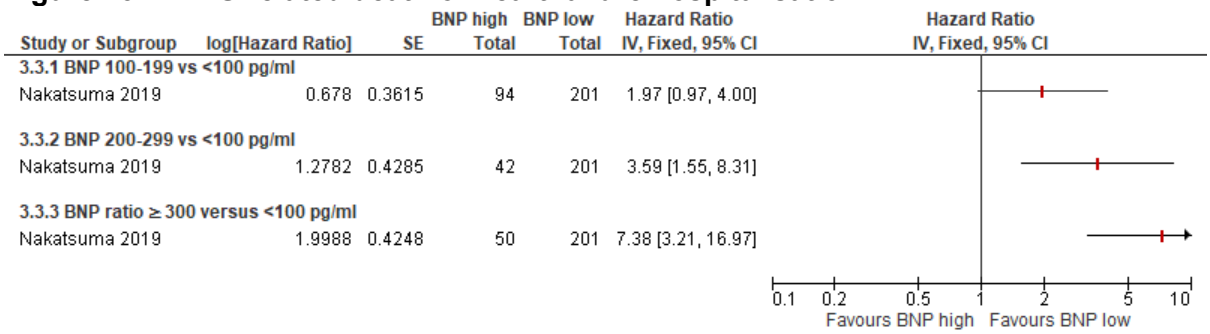
4

Figure 22: Adverse cardiac events



5

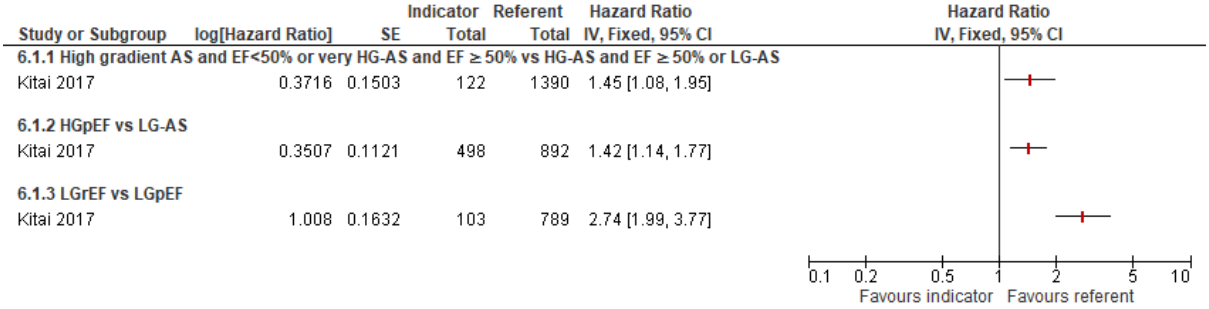
Figure 23: AS-related death or heart failure hospitalisation



6

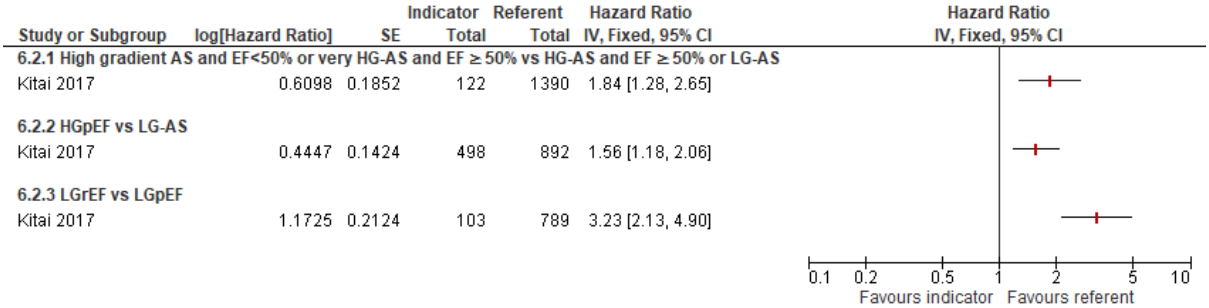
E.1.6 Composite indicators

Figure 24: All-cause mortality



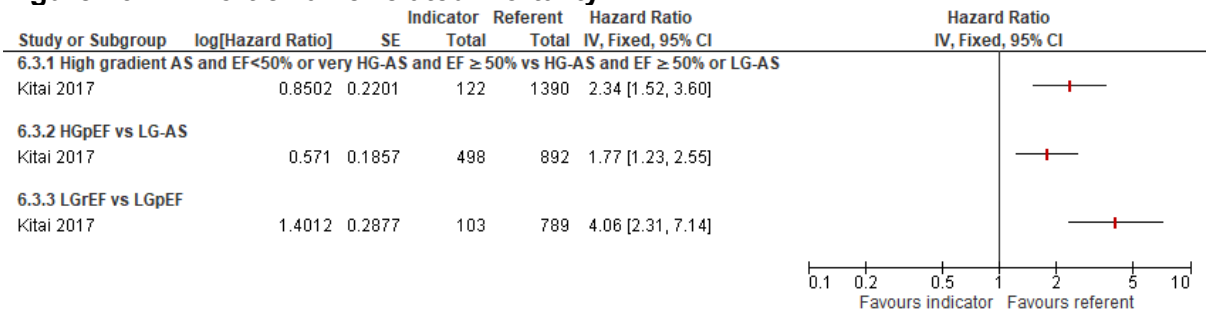
2

Figure 25: Cardiovascular mortality



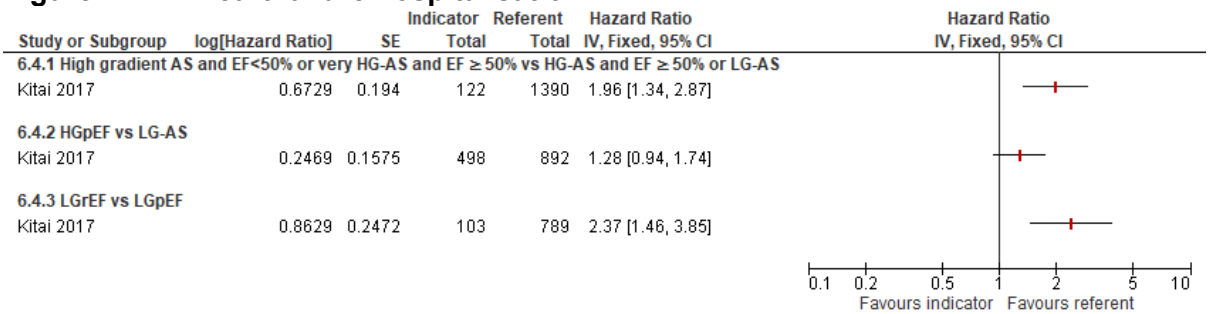
3

Figure 26: Aortic valve-related mortality



4

Figure 27: Heart failure hospitalisation

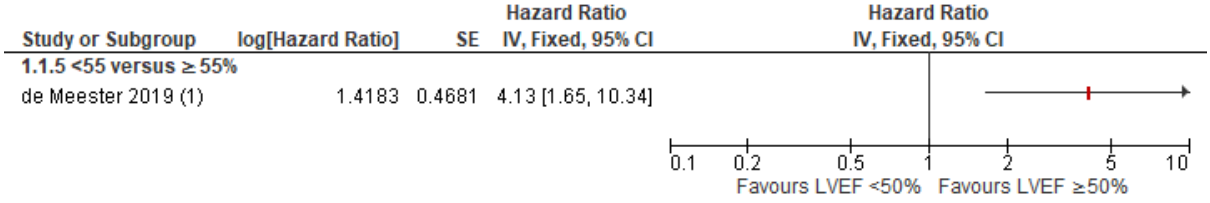


5

E.2 Asymptomatic severe aortic regurgitation

E.2.1 Left ventricular ejection fraction (LVEF): low versus high

Figure 28: Cardiovascular mortality or heart failure



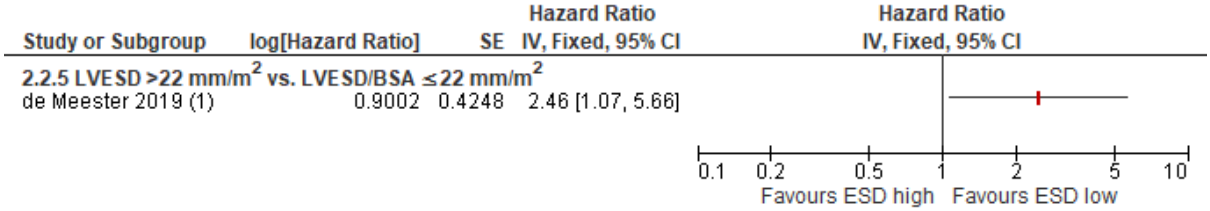
Footnotes
(1) Number in each group not reported

E.2.2 Left ventricular dimensions: high versus low

Figure 29: All-cause mortality (late death)

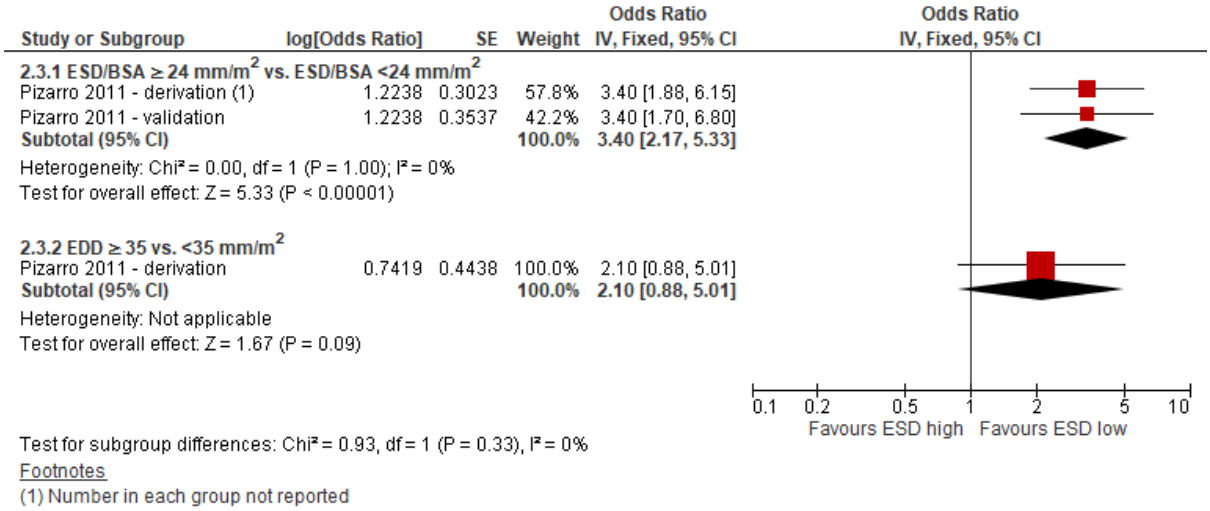
ESDI: Indexed end systolic diameter
EDD: End diastolic diameter

Figure 30: Cardiovascular mortality or heart failure



Footnotes
(1) Number in each group not reported

Figure 31: Left ventricular systolic dysfunction symptoms or death



1

E.2 B-type natriuretic peptide (BNP): increase versus stable

3

Figure 32: Left ventricular systolic dysfunction symptoms or death

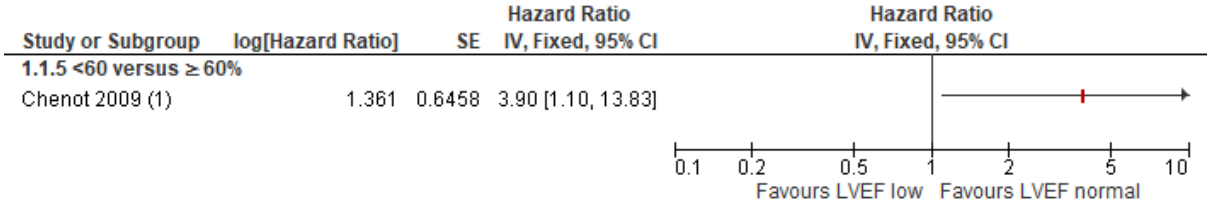
4

E.3 Asymptomatic severe mitral regurgitation

E.3.1 Left ventricular ejection fraction (LVEF): low versus high

7

Figure 33: Cardiac mortality



Footnotes
(1) Number in each group not reported

E.3.2 Left ventricular end systolic diameter (LVESD): high versus low

9

10

Figure 34: Onset of symptoms and/or LV dysfunction

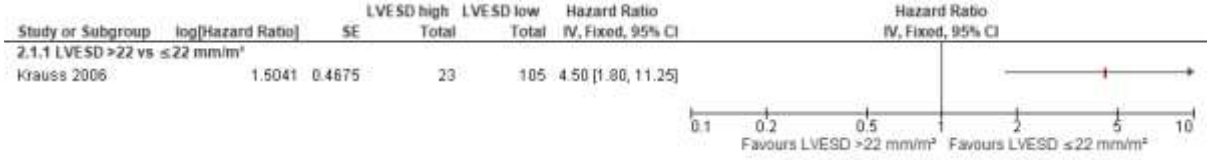
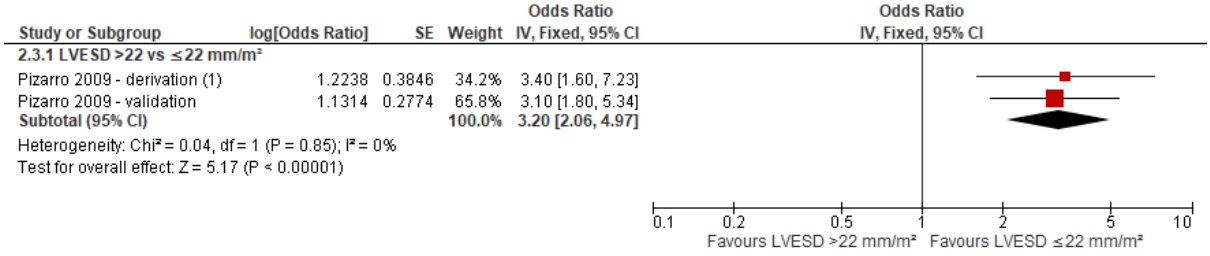


Figure 35: Onset of congestive heart failure, LV dysfunction or death

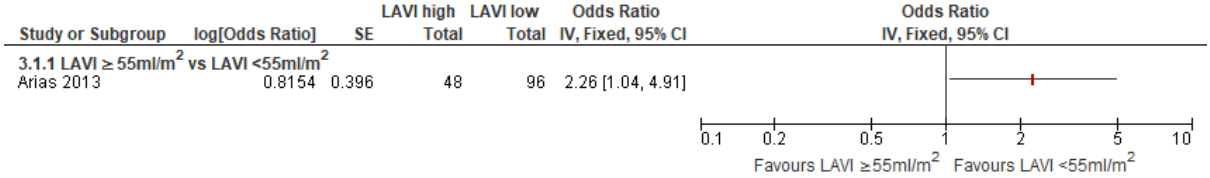


Footnotes
(1) Number in each group not reported for either cohort

Note: Upper limit of 95% CIs calculated in RevMan do not match those reported in the study

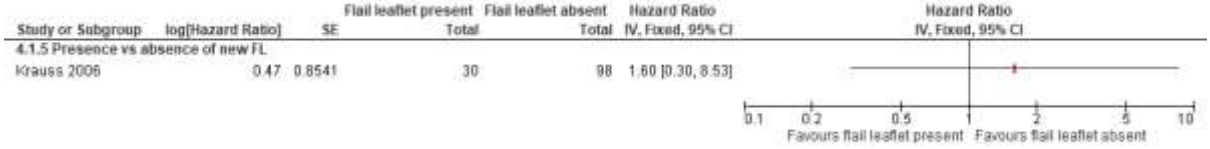
E.3 Left atrial volume index (LAVI): high versus low

Figure 36: Onset of symptoms and/or LV dysfunction



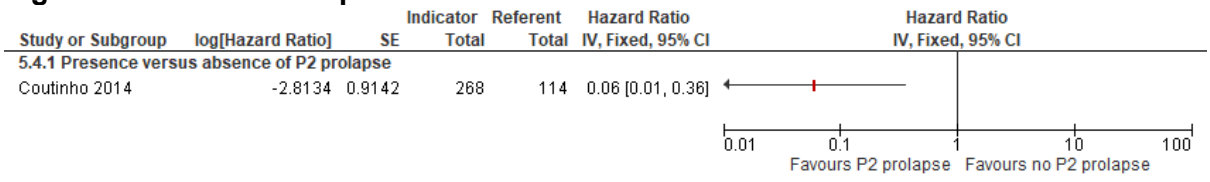
E.4 Flail leaflet

Figure 37: Onset of symptoms and/or LV dysfunction



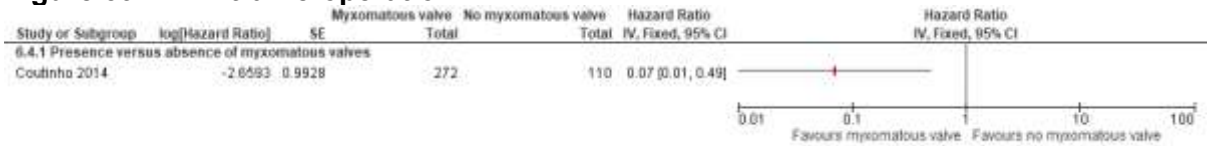
E.5 Posterior prolapse: present versus absent

Figure 38: Mitral re-operation



E.3.6 Ruptured chordae: present versus absent

Figure 39: Mitral re-operation



E.3.7 Atrial fibrillation: present versus absent

Figure 40: Mortality

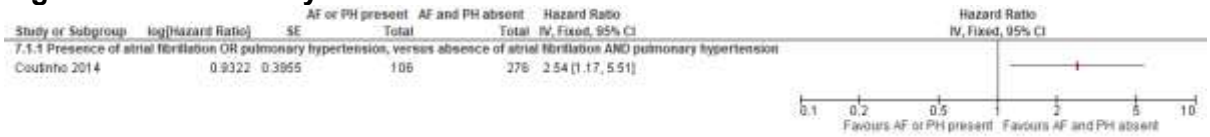


Figure 41: Cardiovascular mortality or mitral valve surgery (repair or replacement) caused by new-onset heart failure

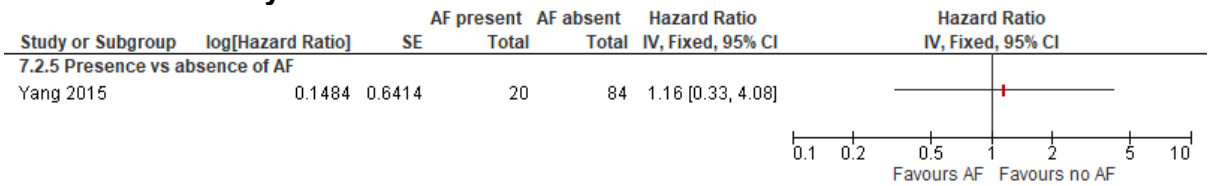


Figure 42: Heart failure

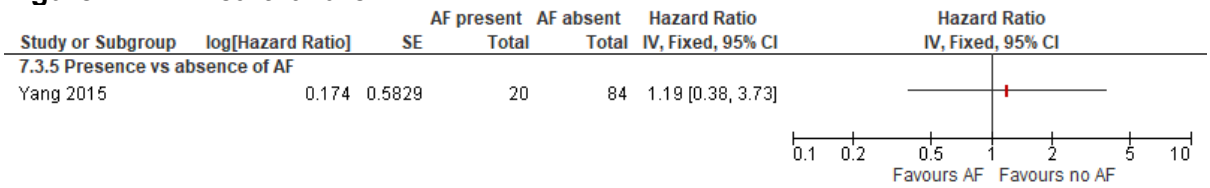


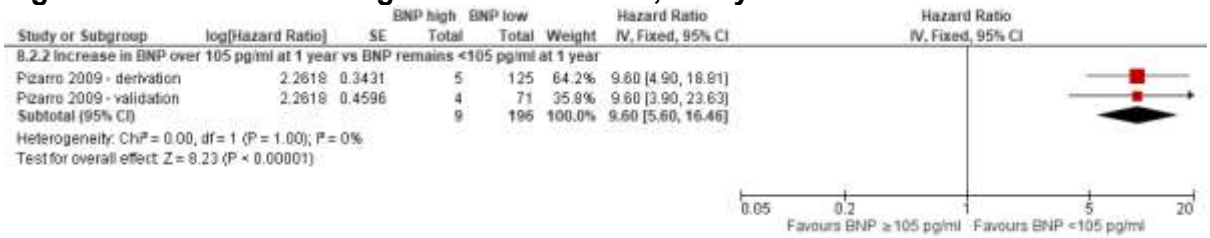
Figure 43: Mitral re-operation

E.3.8 BNP: high versus low

Figure 44: Onset of congestive heart failure, LV dysfunction or death

1 *Note: Upper limit of 95% CIs calculated in RevMan do not match those reported in the study*

Figure 45: Onset of congestive heart failure, LV dysfunction or death



2 *Note: Upper limit of 95% CIs calculated in RevMan do not match those reported in the study*

3

4

5

Appendix F: GRADE tables

F.1 Aortic stenosis

Table 24: Clinical evidence profile: peak aortic jet velocity (Vmax)			Quality assessment				No of patients		Effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Vmax high**	**Vmax low**	**Relative (95% CI)**	
All-cause mortality - ≥5.0 m/s versus <5.0 m/s										
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	272	1147	HR 1.99 (1.51 to 2.62)	⊕⊕⊕O MODERATE
All-cause mortality - Vmax ≥5.5 m/s versus 4-4.49 m/s										
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	65	229	HR 1.2 (1.01 to 1.43)	⊕⊕OO LOW
All-cause mortality - Vmax ≥5.0 m/s versus 4-4.49 m/s										
1	randomised trials	very serious[3]	no serious inconsistency	serious[2]	serious[4]	none	92	364	HR 1.23 (0.83 to 1.82)	⊕OOO VERY LOW
All-cause mortality - Vmax 5.0-5.49 m/s versus 4-4.49 m/s										
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	104	229	HR 1.36 (1.13 to 1.64)	⊕⊕OO LOW
All-cause mortality - Vmax 4.5-4.99 m/s versus 4-4.49 m/s										
2	randomised trials	very serious[3]	serious[5]	no serious indirectness	serious[4]	none	300	593	HR 1.05 (0.63 to 1.74)	⊕OOO VERY LOW
Cardiac or CV mortality - ≥5.0 m/s versus <5.0 m/s										

1	randomised trials	very serious[6]	no serious inconsistency[7]	no serious indirectness	no serious imprecision	none	32	63	HR 1.59 (1.22 to 2.07)	⊕⊕OO LOW
Cardiac or CV mortality - ≥5.0 m/s versus <5.0 m/s										
1	randomised trials	very serious[8]	no serious inconsistency[7]	no serious indirectness	no serious imprecision	none	103	758	HR 6.31 (2.51 to 15.86)	⊕⊕OO LOW
Cardiac or CV mortality - Vmax ≥5.0 m/s versus 4-4.49 m/s										
1	randomised trials	very serious[3]	no serious inconsistency	serious[2]	serious[4]	none	92	364	HR 1.43 (0.88 to 2.32)	⊕OOO VERY LOW
Cardiac or CV mortality - Vmax 4.5-4.9 m/s versus 4-4.49 m/s										
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	140	364	HR 1.27 (0.79 to 2.04)	⊕OOO VERY LOW
Post-AVR mortality - ≥5.0 m/s versus <5.0 m/s										
1	randomised trials	very serious[8]	no serious inconsistency	no serious indirectness	no serious imprecision	none	103	731	HR 2.2 (1.16 to 4.17)	⊕⊕OO LOW
Aortic valve-related mortality - ≥5.0 m/s versus 4-4.49 m/s										
1	randomised trials	very serious[3]	no serious inconsistency	serious[2]	serious[4]	none	92	364	HR 1.69 (0.94 to 3.04)	⊕OOO VERY LOW
Aortic valve-related mortality - Vmax 4.5-4.9 m/s versus 4-4.49 m/s										
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	140	364	HR 1.46 (0.81 to 2.63)	⊕OOO VERY LOW
Heart failure hospitalisation - ≥5.0 m/s versus 4-4.49 m/s										
1	randomised trials	very serious[3]	no serious inconsistency	serious[2]	serious[4]	none	92	364	HR 1.65 (0.97 to 2.81)	⊕OOO VERY LOW
Heart failure hospitalisation - Vmax 4.5-4.9 m/s versus 4-4.49 m/s										

1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	140	364	HR 1.19 (0.73 to 1.94)	⊕OOO VERY LOW
Mortality or AVR - ≥4.5 m/s versus <4.5 m/s										
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	64	62	RR 1.1 (0.7 to 1.73)	⊕OOO VERY LOW
Cardiac mortality or AVR indication - ≥5.5 m/s versus 5.0-5.5 m/s										
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	44	72	HR 1.88 (1.19 to 2.97)	⊕⊕⊕O MODERATE
Cardiac mortality or AVR indication - ≥5.0 m/s versus 4.0-4.9 m/s										
1	randomised trials	very serious[9]	no serious inconsistency	no serious indirectness	no serious imprecision	none	39	64	HR 1.93 (1.16 to 3.21)	⊕⊕OO LOW
Cardiac mortality or AVR indication - >4 m/s versus ≥4.0 m/s										
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	58	45	HR 2.58 (1.15 to 5.79)	⊕⊕OO LOW
Sudden death - ≥5.0 m/s versus <5.0 m/s										
1	randomised trials	very serious[3]	no serious inconsistency	serious[10]	no serious imprecision	none	207	1601	HR 2.36 (1.09 to 5.11)	⊕OOO VERY LOW

[1] Majority of the evidence as at high risk of outcome measurement bias
[2] Indirect threshold comparison
[3] High risk of outcome reporting bias and <10 events per covariable in the analysis
[4] 95% CI crosses the null line
[5] I^2 >75% and only two studies so subgroups could not be explored; random effects model used
[6] High risk of outcome measurement bias and insufficient detail of the statistical analysis
[7] Study differences too great to pool data
[8] High risk of bias from insufficient study participation and high risk of outcome reporting bias
[9] High risk of outcome reporting bias and unclear study participation
[10] Indirect outcome measure

1 **Table 25: Clinical evidence profile: aortic valve area (AVA)**

Quality assessment							No of patients		Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	AVA low	AVA high		
All-cause mortality - AVA≤0.6 versus >0.6 cm²										
1	cohort studies	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	39	190	HR 3.39 (1.8 to 6.38)	⊕⊕OO LOW
All-cause mortality - AVA≤0.6 versus >0.8 cm²										
1	cohort studies	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	199	645	HR 2.61 (1.96 to 3.48)	⊕⊕⊕O MODERATE
All-cause mortality - 0.8≥AVA>0.6 versus >0.8 cm²										
1	cohort studies	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	465	645	HR 1.49 (1.17 to 1.9)	⊕⊕⊕O MODERATE
Cardiovascular mortality - AVA≤0.6 versus >0.8 cm²										
1	cohort studies	very serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	199	645	HR 3.36 (2.34 to 4.82)	⊕⊕OO LOW
Cardiovascular mortality - 0.8≥AVA>0.6 versus >0.8 cm²										
1	cohort studies	very serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	465	645	HR 1.48 (1.07 to 2.05)	⊕⊕OO LOW
Aortic valve-related mortality - AVA≤0.6 versus >0.8 cm²										
1	cohort studies	very serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	199	645	HR 4.53 (2.97 to 6.91)	⊕⊕OO LOW
Aortic valve-related mortality - 0.8≥AVA>0.6 versus >0.8 cm²										

1	cohort studies	very serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	465	645	HR 2.01 (1.31 to 3.08)	⊕⊕OO LOW
Heart failure hospitalisation - AVA≤0.6 versus >0.8 cm²										
1	cohort studies	very serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	199	645	HR 1.95 (1.31 to 2.9) -	⊕⊕OO LOW
Heart failure hospitalisation - 0.8≥AVA>0.6 versus >0.8 cm²										
1	cohort studies	very serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	465	645	HR 1.33 (0.96 to 1.84)	⊕OOO VERY LOW
Cardiac mortality or AVR indication - <0.6 vs. ≥0.6 cm2										
1	cohort studies	serious[2]	no serious inconsistency	no serious indirectness	serious[4]	none	47	69	HR 1.25 (0.77 to 2.03)	⊕⊕OO LOW
Cardiac mortality or AVR indication - <0.75 vs. ≥0.75 cm2										
1	cohort studies	very serious[5]	no serious inconsistency	no serious indirectness	serious[4]	none	Not reported	Not reported	HR 1.48 (0.79 to 2.77)	⊕OOO VERY LOW
Cardiac mortality or AVR indication - AVAI <0.6 vs. ≥0.6 cm2										
1	cohort studies	very serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	66	37	HR 2.62 (1.09 to 6.3)	⊕⊕OO LOW

[1] High risk of bias from stud participation and outcome measurement and <10 events per covariable in the analysis
[2] High risk of bias from outcome measurement
[3] High risk of bias from outcome measurement and <10 events per covariable in the analysis
[4] 95% CI crosses the null line
[5] Inadequate controlling for confounders and high risk of outcome measurement bias

Table 26: Clinical evidence profile: LVEF

Quality assessment		Effect	Quality

							No of patients			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LVEF low**	**LVEF normal**		
All-cause mortality - ≤50 vs >50%										
1	cohort studies	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	104		HR 1.09 (1.03 to 1.15)	⊕⊕OO LOW
All-cause mortality - <55 vs ≥55%										
1	cohort studies	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	239	1439	HR 2.18 (1.6 to 2.97)	⊕⊕⊕O MODERATE
All-cause mortality - <60 versus ≥60%										
1	cohort studies	very serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	267	567	HR 5.01 (2.93 to 8.57)	⊕⊕OO LOW
Cardiovascular mortality - <60 versus ≥60%										
1	cohort studies	very serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	267	567	HR 4.47 (2.06 to 9.7)	⊕⊕OO LOW
Post-AVR mortality - <60 versus ≥60%										
1	cohort studies	very serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	267	567	Only reported as not significant	⊕⊕OO LOW
AS-related death or heart failure hospitalisation at 1 year - <60 versus ≥60%										
1	cohort studies	very serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	168	678	OR 3.94 (2 to 7.76)	⊕⊕OO LOW
Sudden death - <60% vs ≥60%										
1	cohort studies	very serious[4]	no serious inconsistency	serious[5]	no serious imprecision	none	355	1453	HR 1.76 (1.08 to 2.87)	⊕OOO VERY LOW

[1] Unclear prognostic factor measurement, inadequate controlling for confounders and post-hoc selection of thresholds
[2] Unclear if study participation was adequate
[3] High risk of outcome reporting bias and inadequate study participation
[4] High risk of outcome reporting bias and <10 events per covariable in the analysis
[5] Indirect outcome definition

Table 27: Clinical evidence profile: left ventricular global longitudinal strain (LV-GLS)

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LV-GLS	Control			
All-cause mortality - LV-GLS ≤14.7 vs >14.7											
1	cohort studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	345	722	HR 2.62 (1.66 to 4.13)		⊕⊕⊕O MODERATE
All-cause mortality - LVEF ≥6: LV-GLS ≤14.7 vs >14.7											
1	cohort studies	Serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	221	513	HR 2.69 (1.53 to 4.73)		⊕⊕⊕O MODERATE

[1] Unclear if all relevant studies in IPD meta-analysis have been identified and biases in primary studies not assessed or accounted for

Table 28: Clinical evidence profile: BNP

Quality assessment							No of patients		Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BNP high	BNP normal		

All-cause mortality - BNP ratio 1 to 2 versus BNP ratio ≤1										
1	cohort studies	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	130	222	HR 3.02 (1.31 to 6.96)	⊕⊕OO LOW
All-cause mortality - BNP ratio 2 to 3 versus BNP ratio ≤1										
1	cohort studies	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	68	222	HR 4.64 (1.99 to 10.82)	⊕⊕OO LOW
All-cause mortality - BNP ratio ≥3 versus BNP ratio ≤1										
1	cohort studies	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	144	222	HR 3.93 (2.4 to 6.43)	⊕⊕OO LOW
Adverse cardiac events - >20pg/ml/year versus ≤20pg/ml/year										
1	cohort studies	very serious[2]	no serious inconsistency	serious[3]	no serious imprecision	none	34	35	HR 2.73 (1.27 to 5.87)	⊕OOO VERY LOW
Aortic valve-related death of hospitalisation due to HF - BNP 100-199 vs <100 pg/ml										
1	cohort studies	very serious[4]	no serious inconsistency	no serious indirectness	serious[5]	none	94	201	HR 1.97 (0.97 to 4)	⊕OOO VERY LOW
Aortic valve-related death of hospitalisation due to HF - BNP 200-299 vs <100 pg/ml										
1	cohort studies	very serious[4]	no serious inconsistency	serious[6]	no serious imprecision	none	42	201	HR 3.59 (1.55 to 8.31)	⊕OOO VERY LOW
Aortic valve-related death of hospitalisation due to HF - BNP ratio ≥300 versus <100 pg/ml										
1	cohort studies	very serious[4]	no serious inconsistency	serious[6]	no serious imprecision	none	50	201	HR 7.38 (3.21 to 16.97)	⊕OOO VERY LOW

[1] Unclear population source and participation, and <10 event per covariable in the analysis
[2] Insufficient controlling for confounders and unclear method of analysis
[3] Population included some with moderate AS

[4] Inadequate study participation due to lack of BNP data, high risk of outcome reporting bias and inadequate controlling for confounders
[5] 95% CI crosses the null line
[6] Indirect threshold comparison

Table 29: Clinical evidence profile: composite indicators

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Composite indicators	Control			
All-cause mortality - High gradient AS and EF<50% or very HG-AS and EF ≥50% vs HG-AS and EF ≥50% or LG-AS											
1	cohort studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	122	1390	HR 1.45 (1.08 to 1.95)		⊕⊕⊕O MODERATE
All-cause mortality - HGpEF vs LG-AS											
1	cohort studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	498	892	HR 1.42 (1.14 to 1.77)-		⊕⊕⊕O MODERATE
All-cause mortality - LGrEF vs LGpEF											
1	cohort studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	103	789	HR 2.74 (1.99 to 3.77)		⊕⊕⊕O MODERATE
Cardiovascular mortality - High gradient AS and EF<50% or very HG-AS and EF ≥50% vs HG-AS and EF ≥50% or LG-AS											
1	cohort studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	122	1390	HR 1.84 (1.28 to 2.65)		⊕⊕⊕O MODERATE
Cardiovascular mortality - HGpEF vs LG-AS											
1	cohort studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	498	892	HR 1.56 (1.18 to 2.06)-		⊕⊕⊕O MODERATE
Cardiovascular mortality - LGrEF vs LGpEF											

1	cohort studies	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	103	789	HR 3.23 (2.13 to 4.9)-	⊕⊕OO LOW
Aortic valve-related mortality - High gradient AS and EF<50% or very HG-AS and EF ≥50% vs HG-AS and EF ≥50% or LG-AS										
1	cohort studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	122	1390	HR 2.34 (1.52 to 3.6)-	⊕⊕⊕O MODERATE
Aortic valve-related mortality - HGpEF vs LG-AS										
1	cohort studies	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	498	892	HR 1.77 (1.23 to 2.55)-	⊕⊕OO LOW
Aortic valve-related mortality - LGrEF vs LGpEF										
1	cohort studies	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	103	789	HR 4.06 (2.31 to 7.14)-	⊕⊕OO LOW
Heart failure hospitalisation - High gradient AS and EF<50% or very HG-AS and EF ≥50% vs HG-AS and EF ≥50% or LG-AS										
1	cohort studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	122	1390	HR 1.96 (1.34 to 2.87)	⊕⊕⊕O MODERATE
Heart failure hospitalisation - HGpEF vs LG-AS										
1	cohort studies	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	498	892	HR 1.28 (0.94 to 1.74)	⊕⊕OO LOW
Heart failure hospitalisation - LGrEF vs LGpEF										
1	cohort studies	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	103	789	HR 2.37 (1.46 to 3.85)	⊕⊕OO LOW

[1] High risk of outcome reporting bias
[2] High risk of outcome reporting bias and <10 events per covariable in the analysis
[3] 95% CI crosses the null line

F.2 Aortic regurgitation

Table 30: Clinical evidence profile: LVEF

Quality assessment							No of patients		Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LVEF	Control		
Cardiovascular mortality or heart failure - <55 versus ≥55%										
1	cohort studies	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Not reported	Not reported	HR 4.13 (1.65 to 10.34)	⊕⊕OO LOW

[1] High risk of outcome measurement bias and lack of detail on baseline characteristics of asymptomatic group

Table 31: Clinical evidence profile: LVESD

Quality assessment							No of patients		Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LVESD dimensions	Control		
All-cause mortality (late death) - ESDI >25 mm/m2 OR EDD >65 mm vs. ESDI ≤25 mm/m2 AND EDD ≤65 mm										
1	cohort studies	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	101	61	HR 1.99 (0.92 to 4.3)	⊕OOO VERY LOW
Cardiovascular mortality or heart failure - LVESD >22 mm/m2 vs. LVESD/BSA ≤22 mm/m2										
1	cohort studies	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Not reported	Not reported	HR 2.46 (1.07 to 5.66)	⊕⊕OO LOW
LV systolic dysfunction symptoms or death - ESD/BSA ≥24 mm/m2 vs. ESD/BSA <24 mm/m2										

2	cohort studies	very serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	294		OR 3.4 (2.17 to 5.33)	⊕⊕OO LOW
LV systolic dysfunction symptoms or death - EDD ≥35 vs. <35 mm/m2										
1	cohort studies	very serious[4]	no serious inconsistency	no serious indirectness	serious[3]	none	80	80	OR 2.1 (0.88 to 5.01)	⊕OOO VERY LOW

[1] High risk of outcome reporting bias and <10 events per covariable in the analysis
[2] Indirect prognostic factor definition
[3] 95% CI crosses null line
[4] Inadequate description of outcome measurement and recruitment, and inadequate controlling for confounders

Table 32: Clinical evidence profile: BNP

Quality assessment							No of patients		Effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**BNP**	**Control**		
LV systolic dysfunction symptoms or death - BNP increase to ≥130 pg/ml vs retained <130 pg/ml at 1 year										
2	cohort studies	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	7	211	HR 7.89 (4.81 to 12.94)	⊕⊕OO LOW

[1] Inadequate description of outcome measurement and recruitment, and inadequate controlling for confounders

F.3 Mitral regurgitation

Table 33: Clinical evidence profile: LVEF

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LVEF low**	**LVEF high**			

Cardiac mortality - <60 versus ≥60%									
1	cohort studies	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	143	HR 3.9 (1.1 to 13.83)	⊕⊕OO LOW

[1]High risk of outcome measurement bias and inadequate controlling for confounders, and < 10 events per covariable in analysis

Table 34: Clinical evidence profile: LVESD

Quality assessment							No of patients		Effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LVESD high**	**LVESD low**		
Onset of symptoms and/or LV dysfunction - LVESD >22 vs ≤22 mm/m²										
1	cohort studies	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	23	105	HR 4.5 (1.8 to 11.25)	⊕OOO VERY LOW
Onset of symptoms and/or LV dysfunction - LVESD >22 vs ≤22 mm/m²										
1 (2 cohorts)	cohort studies	very serious[3]	no serious inconsistency	serious[2]	no serious imprecision	none	269		OR 3.2 (2.06 to 4.97)[4]	⊕OOO VERY LOW

[1] High risk of outcome measurement bias and inadequate controlling for confounders, and < 10 events per covariable in analysis
[2] Indirect prognostic factor definition
[3] High risk of bias from limitations with study participation and high risk of bias from lack of clarity on confounders adjusted for and likely to be <10 events per covariable in the analysis.
[4] Upper limit of 95% CIs calculated in RevMan do not match those reported in the study

Table 35: Clinical evidence profile: LAVI

Quality assessment							No of patients		Effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LAVI high**	**LAVI low**	**Relative (95% CI)**	

Onset of symptoms or LV dysfunction - LAVI ≥55ml/m2 vs LAVI <55ml/m2										
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	48	96	OR 2.26 (1.04 to 4.88)	⊕OOO VERY LOW

[1] High risk of bias because source population and recruitment are unclear and high risk of bias from inadequate controlling for confounders
[2] Indirect prognostic factor definition

Table 36: Clinical evidence profile: new flail leaflet

Quality assessment							No of patients		Effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Flail leaflet present**	**Flail leaflet absent**		
Onset of symptoms and/or LV dysfunction - Presence vs absence of new FL										
1	cohort studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	30	98	HR 1.6 (0.3 to 8.53)	⊕OOO VERY LOW

[1] High risk of outcome measurement bias and inadequate controlling for confounders, and < 10 events per covariable in analysis
[2] 95% CI crosses null line

Table 37: Clinical evidence profile: posterior prolapse

Quality assessment							No of patients		Effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Posterior prolapse present**	**Posterior prolapse absent**		
Mitral re-operation - Presence versus absence of P2 prolapse										

1	cohort studies	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	268	114	HR 0.06 (0.01 to 0.36)	⊕OOO VERY LOW

[1] High risk of outcome measurement bias and inadequate controlling for confounders, and < 10 events per covariable in analysis
[2] Indirect population (NYHA I and II) and outcome measure

Table 38: Clinical evidence profile: ruptured chordae

Quality assessment							No of patients		Effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Myxomatous valves present**	**Myxomatous valves absent**		
Mitral re-operation - Presence versus absence of myxomatous valves										
1	cohort studies	very serious[1]	no serious inconsistency	very serious[2]	no serious imprecision	none	272	110	HR 0.07 (0.01 to 0.49)	⊕OOO VERY LOW

[1] High risk of outcome measurement bias and inadequate controlling for confounders, and < 10 events per covariable in analysis
[2] Indirect population (NYHA I and II), prognostic factor and outcome definition

Table 39: Clinical evidence profile: atrial fibrillation

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Atrial fibrillation present**	**Atrial fibrillation absent**			
Mortality - Presence of atrial fibrillation OR pulmonary hypertension, versus absence of atrial fibrillation AND pulmonary hypertension											
1	cohort studies	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	106	276	HR 2.54 (1.17 to 5.51)		⊕OOO VERY LOW

Cardiovascular mortality or mitral valve surgery (repair or replacement) caused by new-onset heart failure - Presence vs absence of AF										
1	cohort studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	20	84	HR 1.16 (0.33 to 4.08)-	⊕OOO VERY LOW
Heart failure - Presence vs absence of AF										
1	cohort studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	20	84	HR 1.19 (0.38 to 3.73)	⊕OOO VERY LOW
Mitral re-operation - Presence of atrial fibrillation OR pulmonary hypertension, versus absence of atrial fibrillation AND pulmonary hypertension										
1	cohort studies	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	106	276	HR 4.2 (1.1 to 16.04)-	⊕OOO VERY LOW

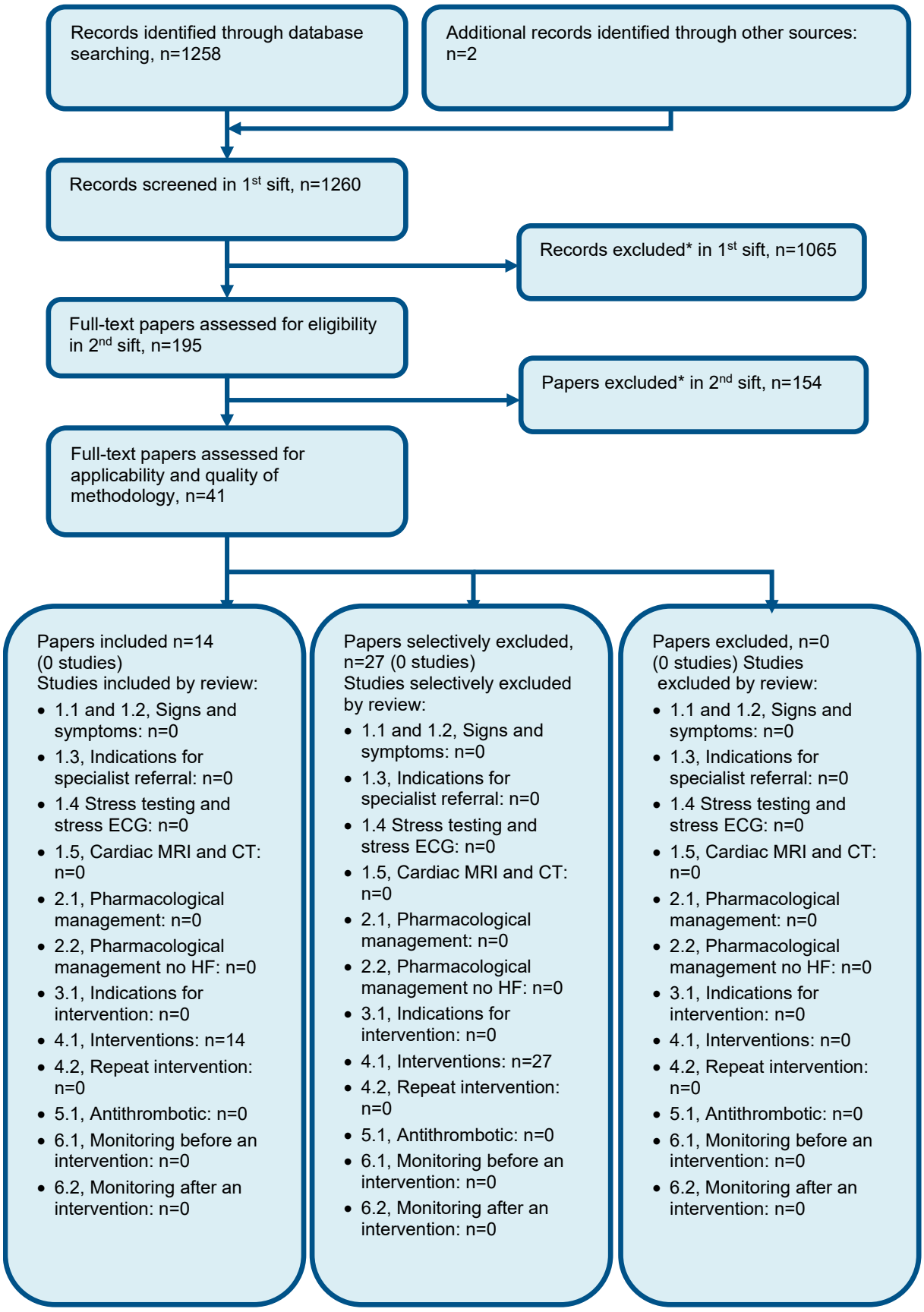
[1] High risk of outcome measurement bias and inadequate controlling for confounders, and < 10 events per covariable in analysis
[2] Indirect population (includes NYHA I and II) and indirect prognostic factor definition
[3] 95% CI crosses the null line

Table 40: Clinical evidence profile: BNP

Quality assessment							No of patients		Effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**BNP high**	**BNP low**	**Relative (95% CI)**	
Onset of CHF, LV dysfunction or death - BNP ≥105 pg/ml vs BNP <105 pg/ml										
1 (2 cohorts)	cohort studies	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	64	205	OR 4.28 (3.08 to 5.95)[3]	⊕OOO VERY LOW
Onset of CHF, LV dysfunction or death - Increase in BNP over 105 pg/ml at 1 year vs BNP remains <105 pg/ml at 1 year in subgroup with BNP <105 pg/ml at baseline										
1 (2 cohorts)	cohort studies	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	9	196	HR 9.6 (5.6 to 16.46)[3]	⊕⊕OO LOW

[1] High risk of bias from limitations with study participation and high risk of bias from lack of clarity on confounders adjusted for and likely to be <10 events per covariable in the analysis.
[2] Indirect prognostic factor definition
[3] Upper limit of 95% CIs calculated in RevMan do not match those reported in the study

Appendix G: Health economic evidence selection



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

1

Appendix H: Health economic evidence tables

None

Appendix I: Excluded studies

I.1 Excluded clinical studies

Table 41: Studies excluded from the clinical review

Reference	Reason for exclusion
Abdel Fattah 2016[1]	Incorrect study design: no multivariable analysis; only reports sensitivity and specificity
Alashi 2016[4]	Incorrect prognostic factors: only analysed as continuous variables for factors of interest (no thresholds assessed) Inadequate adjustment for confounders
Alashi 2018[3]	Incorrect prognostic factors: only analysed as continuous variables for factors of interest (no thresholds assessed)
Alashi 2020[2]	Incorrect prognostic factors: only analysed as continuous variables for factors of interest (no thresholds assessed)
Antonini-Canterin 2018[5]	Insufficient reporting of results
Avakian 2008[7]	Incorrect outcomes
Avierinos 2002[8]	Incorrect population: mitral valve prolapse - not severe MR)
Badhwar 2012[9]	Incorrect population: majority symptomatic with no separate results for asymptomatic group)
Badran 2012[10]	Incorrect population: majority symptomatic and no separate prognostic analysis performed for the asymptomatic group
Bahler 2018[11]	Incorrect outcomes, and no multivariable analysis
Banovic 2015[12]	Incorrect prognostic factors: only analysed as continuous variables for factors of interest (no thresholds assessed)
Banovic 2016[13]	Incorrect study design: not prognostic study
Banovic 2020[14]	Incorrect prognostic factors and outcomes - none matching protocol
Barbieri 2020[15]	Incorrect prognostic factors - none matching protocol
Baumgartner 2020[16]	Narrative review - references checked
Bergler-Klein 2004[17]	Incorrect prognostic factors: only analysed as continuous variables for factors of interest (no thresholds assessed)
Bergstra 2020[18]	Narrative review - references checked
Bhattacharyya 2012[19]	Narrative review: references checked.
Bhudia 2007[20]	Incorrect population: majority symptomatic and no separate results for asymptomatic group)
Biem 1990[21]	Incorrect study design: decision analysis
Bijvoet 2020[22]	Systematic review - inadequate quality assessment of included studies
Biner 2010[23]	Incorrect population and analysis: no multivariable analysis for suitable prognostic factors in the asymptomatic subgroup

Reference	Reason for exclusion
Bing 2019[24]	Protocol only
Bohbot 2017[28]	Incorrect prognostic factor: mean trans-aortic pressure gradient
Bohbot 2018[29]	Incorrect study design: no prognostic analysis - only comparison of intervention strategies)
Bohbot 2019[25]	Incorrect population <75% were asymptomatic
Bohbot 2020[27]	Incorrect prognostic factor – not matching protocol
Bonow 1983[33]	Incorrect analysis: no multivariable analysis
Bonow 1985[32]	Incorrect population: no separate analyses for asymptomatic subgroup
Bonow 1991[31]	Incorrect analysis: only reports likelihood percentages
Borer 1998[34]	Incorrect analysis: no multivariable analysis
Brown 2008[35]	Incorrect prognostic factors
Calin 2020[36]	Narrative review - references checked
Calleja 2010[37]	Incorrect comparison
Cameli 2019[38]	Incorrect population: all moderate severity; and incorrect prognostic factors: none matching protocol
Capoulade 2014[40]	Incorrect prognostic factors: only analysed as continuous variables for factors of interest (no thresholds assessed)
Carabello 1986[43]	Incorrect population: all symptomatic.
Carabello 1995[41]	Narrative review: references checked
Carabello 2012[42]	Narrative review: references checked
Carasso 2015[44]	Incorrect comparison
Carstensen 2016[45]	Incorrect prognostic factors: only analysed as continuous variables for factors of interest (no thresholds assessed)
Casaclang-Verzosa 2010[46]	Incorrect prognostic factor
Casas-Rojo 2016[47]	Incorrect study design: no multivariate analysis for relevant prognostic factors
Chaliki 2002[49]	Incorrect population: mixed symptomatic and asymptomatic - no separate results for asymptomatic group
Chaliki 2007[48]	Narrative review: references checked
Cheitlin 2005[50]	Incorrect study type: narrative review, references checked
Cho 2019[52]	Incorrect population: not severe and >25% of the population symptomatic rather than asymptomatic
Cimadevilla 2013[53]	Incorrect population: <50% asymptomatic and only 64% severe (no subgroup analysis for asymptomatic severe)
Cioffi 2011[54]	Incorrect prognostic factors
Cioffi 2016[55]	incorrect prognostic factor
Colli 2018[57]	Insufficient reporting of results
Coutinho 2016[58]	Indirect population: >25% symptomatic. Also available prognostic factors do not match our thresholds
Cramariuc 2009[60]	Incorrect population (unclear severity) and prognostic factors

Reference	Reason for exclusion
Dahl 2012[61]	Included in IPD meta-analysis
Dal-Bianco 2008[62]	Narrative review: references checked
De Jesus 2020[63]	Incorrect outcome measure – LVEF decrease after intervention
de Meester 2015[65]	Incorrect prognostic factors
Delesalle 2019[66]	Incorrect population: moderate aortic stenosis rather than severe
Detaint 2005[67]	Incorrect population - 35% severe
Detaint 2008[68]	Insufficient information reported to extract (i.e. no HR or RR within the severe population specifically)
Dorros 1990[69]	Incorrect population: all symptomatic severe.
Dujardin 1999[70]	Incorrect population: mixed symptomatic and asymptomatic
Dulgheru 2012[71]	Narrative review: references checked
Dupuis 2017[72]	Incorrect population: mixture of different severities.
Egbe 2018[73]	Incorrect population: moderate mixed aortic valve disease
El Sabbagh 2019[74]	Incorrect population: all symptomatic.
Enache 2010[75]	Incorrect analysis: no adjustment for confounders
Enriquez-Sarano 1994[78]	Incorrect population: majority are symptomatic and no separate analyses for asymptomatic subgroup
Enriquez-Sarano 1994[79]	Incorrect/unclear population: severity and symptom status unclear
Enriquez-Sarano 2005[76]	Incorrect population (43% with severe MR) and prognostic factors
Enriquez-Sarano 2015[77]	Incorrect prognostic factors
Errichetti 1990[80]	Incorrect study type: narrative review (references checked)
Ewe 2015[81]	Incorrect analysis (sensitivity/specificity - no univariate or multivariate analysis) and population (unclear proportion with severe AS in the asymptomatic group)
Farre 2014[82]	Incorrect definition of prognostic factor and result only presented graphically for population of interest
Feuchtner 2006[83]	Incorrect study design: no multivariate analysis (correlation only)
Flint 2020[84]	Narrative review - references checked
Forman 1980[85]	Incorrect population: all symptomatic
Fries 2017[86]	Incorrect population (majority symptomatic and no separate analysis for asymptomatic group)
Gaasch 1983[87]	Incorrect population: majority symptomatic and no separate analysis for asymptomatic group Incorrect analysis: only sensitivity/specificity values reported
Gaasch 1995[88]	Incorrect study type: narrative review (references checked)
Gahl 2020[89]	Systematic review - references checked

Reference	Reason for exclusion
Genereux 2016[90]	Narrative review: references checked
George 2019[91]	Incorrect prognostic factors: only analysed as continuous variables for factors of interest (no thresholds assessed)
Gerber 2003[93]	Incorrect prognostic factors: compares BNP levels in those with/without symptoms. No prognostic assessment for outcomes.
Gerber 2005[92]	Incorrect outcome measure
Gerber 2020[94]	Incorrect study design - no prognostic analysis
Gerdts 2015[95]	Incorrect population: mild to moderate rather than severe AS
Gillam 2014[96]	Incorrect study type: narrative review (references checked)
Giritharan 2019[97]	Protocol for study not yet started
Gohlke-Barwolf 2013[98]	Incorrect population: mild/moderate AS
Goldstone 2015[99]	Incorrect study design: SR for interventions. References checked.
Gomez Perez 2017[100]	Incorrect analysis: only sensitivity/specificity values reported
Gozdzik 2019[101]	Narrative review: references checked
Greves 1981[102]	Incorrect population: majority symptomatic Incorrect analysis: no prognostic analysis with multivariate analysis
Grigioni 1999[103]	Incorrect population: mixture of asymptomatic and symptomatic
Hachicha 2007[104]	Incorrect population (includes symptomatic) and analysis (only univariate analysis for relevant factors)
Hachicha 2009[105]	Incorrect prognostic factors Indirect population: moderate-severe aortic stenosis
Henkel 2012[106]	Incorrect prognostic factors: only gives HRs for whether or not had intervention
Henry 1980[108]	Incorrect study design: does not perform univariate or multivariate analysis for the prognostic factors mentioned, just compares narratively the outcomes for different subgroups. Also severity unclear.
Hering 2004[109]	Incorrect population (not severe) and incorrect study design (no multivariable analysis)
Hristova-Antova 2009[110]	Incorrect study design: only univariate analysis
Hu 2020[111]	Incorrect outcomes - none matching protocol
Huded 2018[112]	Incorrect prognostic factors: only analysed as continuous variables for factors of interest (no thresholds assessed)
Ilardi 2020[113]	Incorrect prognostic factors: only analysed as continuous variables for factors of interest (no thresholds assessed) Also predictors of outcome performed on the whole cohort not separately for the asymptomatic group
Imai 2008[114]	Incorrect population: <50% severe)

Reference	Reason for exclusion
	Incorrect prognostic factors: all those looked at continuous, looks for associations with severity rather than outcomes
Iung 1996[116]	Incorrect population: majority symptomatic and no separate results for asymptomatic group
Iung 2007[115]	Incorrect study design: not prognostic MVA for severe asymptomatic population
Izumo 2017[117]	Incorrect prognostic factors and population: predictors not assessed only in asymptomatic population and only continuous prognostic factors used
Jansen 2018[118]	Incorrect study design/report type
Kaleschke 2011[119]	Literature review: references checked
Kanamori 2018[120]	Incorrect prognostic factors: symptomatic vs. asymptomatic status on outcomes
Kang 2009[122]	Incorrect prognostic factors: only analysed as continuous variables for factors of interest (no thresholds assessed)
Kang 2012[123]	Incorrect prognostic factors: only analysed as continuous variables for factors of interest (no thresholds assessed)
Kang 2014[126]	Incorrect study design - compares outcomes between two interventions. Not prognostic factors for outcomes.
Kang 2020[124]	Incorrect study design - compares outcomes between two interventions. Not prognostic factors for outcomes.
Kearney 2012 [127]	Included in IPD meta-analysis
Kelly 1988[128]	Incorrect comparison: symptom status
Kim 2019[129]	Incorrect prognostic factors
Kitai 2011[130]	Incorrect prognostic factors/analysis (univariate) - also not performed in asymptomatic subgroup only
Klaar 2011[132]	Incorrect prognostic factors: only analysed as continuous variables for factors of interest (no thresholds assessed)
Klodas 1997[133]	Incorrect population: mixture of asymptomatic and symptomatic
Kockova 2019[134]	Incorrect outcomes - none matching protocol
Kusunose 2014[136]	Incorrect prognostic factors: only analysed as continuous variables for factors of interest (no thresholds assessed) Included in IPD meta-analysis
Lancellotti 2010[137]	Incorrect population: unclear proportion with severe/moderate disease. Incorrect analysis: no MVA outcomes reported for threshold values
Lancellotti 2010[141]	Incorrect prognostic factors: those included in MVA only continuous, no thresholds. Only AUC, sensitivity and specificity mentioned for some prognostic thresholds
Lancellotti 2012[138]	Incorrect prognostic factors: only analysed as continuous variables for factors of interest (no thresholds assessed)
Lancellotti 2012[139]	Incorrect prognostic factor: SPAP >60 on exercise rather than at rest

Reference	Reason for exclusion
Laurenzano 2019[142]	Incorrect prognostic factors and outcomes - none matching protocol
Le Tourneau 2010[143]	Incorrect study design - no multivariate analysis for the severe subgroup
Le Tourneau 2010[144]	Incorrect prognostic factors
Le Tourneau 2010[145]	Incorrect population: mixed asymptomatic and symptomatic, and severity of MR unclear
Lee 2013[146]	Incorrect population: all symptomatic AS
Lee 2017[147]	Incorrect population: moderate disease, and mixed AS/AR Incorrect prognostic factors
Levine 1990[148]	Incorrect study type: narrative review (references checked)
Levy-Neuman 2019[149]	Incorrect prognostic factor definitions and outcomes
Lim 2004[150]	Incorrect prognostic factors: only analysed as continuous variables for factors of interest (no thresholds assessed)
Lim 2017[151]	Incorrect study design: not a prognostic study review. References checked
Lindman 2018[152]	Incorrect population: not asymptomatic
Lindman 2020[153]	Narrative review – references checked
Ling 1996[154]	Incorrect population (majority symptomatic) and prognostic factors (none matching form of factors in protocol)
Ma 2019[155]	Incorrect population: not severe MR
Maes 2014[157]	Incorrect prognostic factors: only analysed as continuous variables for factors of interest (no thresholds assessed)
Magne 2010[159]	Incorrect population (only 60% severe) and analysis (only adjusted for age and sex on MVA)
Magne 2012[161]	Incorrect population (only 63% severe) and prognostic factors (exercise variables)
Magne 2012[162]	Incorrect population - some with moderate rather than severe disease (only 61% severe). No separate analysis for those with severe disease.
Magne 2014[160]	Incorrect population (only 63% severe) and prognostic factors (exercise variables)
Magne 2015[163]	Incorrect population (50% with symptoms and no separate analysis) and prognostic factors (none in form matching protocol)
Malouf 2012[164]	Incorrect population: majority symptomatic and unclear severity - likely mixture of mild-severe
Marechaux 2010[165]	Incorrect prognostic factors: only analysed as continuous variables for factors of interest (no thresholds assessed)
Marechaux 2019[167]	Incorrect prognostic factors - none matching protocol
Marwick 2013[168]	Incorrect study design: Markov model (for HE)
Mateescu 2019[169]	Incorrect outcomes

Reference	Reason for exclusion
Mathieu 2017[170]	Incorrect prognostic factors: only analysed as continuous variables for factors of interest (no thresholds assessed)
Matos 2017[171]	Incorrect prognostic factors (none matching protocol) and population (moderate-severe included)
Mentias 2016[173]	Incorrect prognostic factors: only analysed as continuous variables or unadjusted analysis for factors of interest (no thresholds assessed)
Mentias 2016[174]	Incorrect prognostic factors: only analysed as continuous variables for factors of interest (no thresholds assessed)
Mentias 2016[172]	Incorrect prognostic factors: none matching the protocol
Messika-Zeitoun 2004[176]	Incorrect population: only 69% with severe TR in the asymptomatic group. Incorrect analysis: comparison with matched general population sample
Messika-Zeitoun 2007[175]	Incorrect population - 52% severe
Michelena 2008[177]	Incorrect population: limited to no or mild stenosis/regurgitation
Miller 2013[178]	narrative review: references checked
Miura 2019[181]	Incorrect study design: intervention study with no prognostic analysis
Miura 2020[180]	Incorrect population - <75% were asymptomatic
Miyake 2018[182]	Incorrect study design (no MVA analysis)
Monin 2009[183]	Incorrect population (only 72% severe disease) and prognostic factors (only analysed as continuous variables for factors of interest (no thresholds assessed)
Montant 2009[184]	Incorrect prognostic factors: only analysed as continuous variables for factors of interest (no thresholds assessed)
Morimoto 2019[185]	Incorrect prognostic factor
Nagata 2015[186]	Incorrect prognostic factors: only analysed as continuous variables for factors of interest (no thresholds assessed) or only provide sensitivity/specificity for thresholds
Namisaki 2019[189]	Incorrect prognostic factor: symptom status (for 1.3)
Nessmith 2005[191]	Incorrect population (no results separately for the asymptomatic subgroup) and prognostic factors (only analysed as continuous variables for factors of interest (no thresholds assessed))
Ng 2018[192]	Incorrect population: >50% with symptoms
Nguyen 2017[193]	Incorrect reporting: p-values and graphs only for relevant analysis; Incorrect population: all severities and with or without symptoms
Nistri 2012[195]	Incorrect population (only 12% severe disease) and prognostic factors (only analysed as continuous variables for factors of interest (no thresholds assessed))
O'Gara 2018[196]	Incorrect study design: editor's note
Ogutu 2010[197]	Systematic review with no relevant data to extract. Also methods inadequate. References checked.

Reference	Reason for exclusion
Otto 1997[198]	Incorrect population - unclear whether all were severe at start of study. Incorrect analysis: no multivariable or adjusted results reported.
Owen 2011[199]	Narrative review: references checked
Pai 2006[200]	Incorrect prognostic factors: only analysed as continuous variables for factors of interest (no thresholds assessed)
Pellikka 1990[201]	Incorrect analysis: not adjusted
Pellikka 2005[202]	Incorrect analysis: Only univariate results given for factor of interest
Percy 1993[203]	Incorrect study design: case-control and unadjusted
Perera 2011[204]	Incorrect study design: no prognostic analysis
Pierri 2000[205]	Incorrect prognostic factors
Pineda 2018[206]	Literature review: references checked
Piper 2003[207]	Incorrect population, prognostic factors and outcomes/analysis
Potter 2018[210]	Narrative review: references checked
Rajani 2009[211]	Incorrect population (not limited to severe AS) and analysis (no MVA performed for suitable prognostic factors). Also indirect outcomes.
Ramos 2019[212]	Incorrect analysis - univariate only and insufficient reporting
Rashedi 2014[213]	Incorrect population: all severities
Recke 1993[214]	Incorrect population: all symptomatic
Rezzoug 2015[215]	Incorrect population (not all asymptomatic) and prognostic factors
Roseman 1965[216]	Incorrect study design: no prognostic analysis
Rosen 1994[217]	Incorrect prognostic factors
Rosenhek 2002[221]	Narrative review: references checked
Rosenhek 2004[220]	Incorrect population: mild and moderate AS
Rosenhek 2006[222]	Incorrect study design (no prognostic analysis)/ incorrect prognostic factors (none relevant to protocol). No adjusted HR/RRs reported, only survival mentioned
Rosenhek 2011[218]	Narrative review: references checked
Rubattu 2020[224]	Editorial only - references checked
Rusinaru 2011[225]	Incorrect prognostic factor - left atrial diameter, not volume
Sa 2019[226]	Systematic review: references checked
Saeed 2020[227]	Incorrect prognostic factors - none matching protocol
Saeed 2020 [228]	Incorrect prognostic factors - none matching protocol
Salaun 2018[230]	Included in IPD meta-analysis
Samuels 1979[231]	Incorrect population (majority symptomatic and severity unclear) and study design (no univariate or multivariate prognostic analysis performed)
Sato 2014[232]	Included in IPD meta-analysis

Reference	Reason for exclusion
Sharma 2014[233]	Incorrect population (includes those with symptoms) and prognostic factors (those matching protocol only univariate analysis)
Shibayama 2016[234]	Incorrect prognostic factors - either not mentioned in our protocol or continuous values rather than thresholds
Shirai 2017[235]	Incorrect prognostic factors
Sia 2020[236]	Incorrect prognostic factors - none matching protocol
Siemienczuk 1989[237]	Incorrect outcome and analysis (univariate only) and incorrect population (severity not stated)
Sinha 2016[238]	Incorrect study design: no multivariate analysis
Stahle 1997[239]	Incorrect population: all symptomatic and severity unclear, mixed stenosis/regurgitation Incorrect prognostic factors: none matching protocol
Stewart 2010[240]	Incorrect population (moderate to severe), prognostic factors (all continuous with no thresholds) and outcome (not in protocol)
Sun 2019[241]	Incorrect population: majority not severe valve disease
Suzuki 2018[242]	Incorrect prognostic factor (severity)
Takeda 2001[243]	Incorrect population and prognostic factor definitions
Taniguchi 2015[245]	Incorrect study design: intervention comparisons with no prognostic analysis
Taniguchi 2016[247]	Incorrect population: does not perform MVA for the asymptomatic group separately
Taniguchi 2020[246]	Narrative review – references checked
Tarasoutchi 1999[248]	Incorrect prognostic factor and outcomes
Tarasoutchi 2003[249]	insufficient reporting and incorrect outcome
Tastet 2019[250]	Incorrect population: only 61% severe
Teraguchi 2020[251]	Incorrect analysis - univariate only
Thakker 2020[252]	Incorrect population – all symptomatic
Thomassen 2017[254]	Incorrect population: not all severe - combined with moderate severity No suitable prognostic factors.
Thompson 1982[255]	Incorrect study design: no prognostic assessment.
Tietge 2012[256]	Incorrect study design: protocol only and RCT not completed yet
Todaro 2016[257]	Incorrect prognostic factors: only analysed as continuous variables for factors of interest (no thresholds assessed)
Tomsic 2018[258]	Incorrect study type: no prospective data and case-control vs general population)
Tornos 1990[260]	Incorrect study design: no MVA and incorrect comparison (symptom status (Q1.3)
Tornos 1995[259]	Incorrect outcome: need for surgery

Reference	Reason for exclusion
Tornos 2006[261]	Incorrect study design: no adjustment for confounders
Tribouilloy 1999[264]	Incorrect comparison: symptomatic vs asymptomatic
Tribouilloy 2009[262]	Incorrect population: not all severe and <40% asymptomatic
Tribouilloy 2011[263]	Incorrect population: 14% NYHA 1
Turina 1984[265]	Incorrect population (majority with symptoms) and study design (no apparent prognostic analysis)
Vaquette 2005[266]	Incorrect population: majority symptomatic
Varadarajan 2006[267]	Incorrect population: 47% symptomatic
Verseckaite 2018[268]	Incorrect prognostic factors: only analysed as continuous variables for factors of interest (no thresholds assessed)
Vollema 2018[269]	Incorrect analysis: no adjusted HRs given and insufficient information to extract or calculate
Wang 2016[271]	Incorrect prognostic factors: only analysed as continuous variables for factors of interest (no thresholds assessed)
Wang 2017[270]	Incorrect study design: comparison of interventions with no prognostic factor analysis
Wilson 1992[272]	Incorrect population (majority congenital and unclear severity, also mixture of those with/without symptoms) and prognostic factors (no thresholds or adjusted effect measures given)
Wisenbaugh 1986[273]	Incorrect population: all symptomatic
Wisenbaugh 1994[274]	Incorrect population: all symptomatic
Wu 2018[275]	Incorrect prognostic factors: only analysed as continuous variables for factors of interest (no thresholds assessed)
Yingchoncharoen 2012[277]	Incorrect prognostic factors: only analysed as continuous variables for factors of interest (no thresholds assessed)
Yousof 1988[278]	Incorrect study design: no prognostic analysis using MVA
Zhao 2013[279]	Incorrect study design: watchful waiting versus early surgery
Zhou 2018[280]	Incorrect population: no MVA analysis for suitable prognostic factors performed in the asymptomatic subgroup.
Zito 2011[282]	Incorrect prognostic factors: only analysed as continuous variables for factors of interest (no thresholds assessed)
Zlotnick 2013[283]	Incorrect population: not asymptomatic

1

I.2 Excluded health economic studies

1.7.1 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 J: Research recommendations

J.1 BNP

J.1.1 Research question:

Research question: In adults with asymptomatic, severe aortic regurgitation or mitral regurgitation what is the prognostic value and cost effectiveness of BNP to assess the need for intervention?

J.1.2 Why this is important:

Asymptomatic aortic and mitral regurgitation can be challenging for doctors to manage. The optimal time for valve surgery/intervention would be just before symptoms develop - once symptoms have occurred, intervention is indicated, but it is thought that outcomes are slightly worse by this stage. BNP (B-type natriuretic peptide) is a hormone released by the heart, which can indicate the myocardium (heart muscle) is under strain. Blood levels of BNP could be a sensitive indicator of cardiac decompensation, prior to the onset of symptoms. It is already used by GPs to identify potential patients with heart failure, and it could be a readily accessible method for assessment of asymptomatic patients with severe heart valve disease in general practice.

The committee did not consider that the available evidence was of sufficient quality or quantity to recommend the use of BNP to identify suitable patients for intervention with asymptomatic severe aortic and mitral regurgitation.

J.1.3 Rationale for research recommendation

Importance to patients or the population	If BNP was demonstrated to be effective at identifying patients with a better prognosis following intervention, it could result in earlier intervention being offered to patients, with better outcomes (mortality, fewer episodes of heart failure) following intervention.
Relevance to NICE guidance	There is current uncertainty about the benefit of earlier intervention based on BNP levels.
Relevance to the NHS	Research in this area would inform NICE recommendations on the use of global longitudinal strain for indicating suitable patients for intervention while asymptomatic.
Current evidence base	Limited evidence was identified. Further studies are needed to inform recommendations on the role of BNP in the prognosis of people with aortic and mitral regurgitation?
Equality considerations	Younger patients (under 50 years) have greater physical reserve and tend to become symptomatic at a late stage of the disease. They would particularly benefit from tests that identify early cardiac decompensation, before symptoms develop.

J.12.4 Modified PICO table

Population	Inclusion Adults aged 18 years and over with diagnosed severe heart valve disease that is asymptomatic, stratified by the type of heart valve disease as follows: • aortic regurgitation • mitral regurgitation Exclusion • Children (aged <18 years)
Prognostic variable	• BNP increase at serial measurements (without other explanation)
Confounding factor	• Surgical risk scores (e.g. EuroScore I or II, STS) • Age • Sex • Renal impairment • Previous cardiac surgery • Diabetes • Hypertension • Atrial fibrillation • Prior MI • Active endocarditis • Frailty scores (e.g. CSHA, Katz score)
Outcome	• Mortality (≥12 months from surgery) • Hospital admission for heart failure (≥12 months from surgery)
Study design	Cohort Randomised controlled trial would provide the strongest evidence
Timeframe	Long term
Additional information	None

J.2 Global longitudinal strain

J.2.1 **Research question:** In adults with severe heart valve disease what is the prognostic value and cost effectiveness of global longitudinal strain to assess the need for intervention?

J.2.2 Why this is important:

Asymptomatic severe heart valve disease can be challenging for doctors to manage. The optimal time for valve surgery/intervention would be just before symptoms develop - once symptoms have occurred, intervention is indicated, but it is thought that outcomes are slightly worse by this stage. Global longitudinal strain is an echocardiographic technique that provides advanced assessment of the pumping function (contractility) of the heart, and could be a more sensitive technique for identifying the very early stages of cardiac decompensation, prior to the onset of symptoms.

The committee did not consider that the available evidence was of sufficient quality or quantity to recommend the use of global longitudinal strain to identify suitable patients for intervention with asymptomatic severe heart valve disease.

J.243 Rationale for research recommendation

Importance to patients or the population	If global longitudinal strain was demonstrated to be effective at identifying patients with a better prognosis following intervention, it could result in earlier intervention being offered to patients, with better outcomes (mortality, fewer episodes of heart failure) following intervention.
Relevance to NICE guidance	There is current uncertainty about the benefit of earlier intervention based on global longitudinal strain measures.
Relevance to the NHS	Research in this area would inform NICE recommendations on the use of global longitudinal strain for indicating suitable patients for intervention while asymptomatic.
Current evidence base	Limited evidence was identified. Further studies are needed to inform recommendations on the role of global longitudinal strain in the prognosis of adults with asymptomatic, severe heart valve disease.
Equality considerations	Younger patients (under 50 years) have greater physical reserve and tend to become symptomatic at a late stage of the disease. They would particularly benefit from imaging techniques that identify early cardiac decompensation, before symptoms develop.

J.254 Modified PICO table

Population	Inclusion Adults aged 18 years and over with diagnosed severe heart valve disease that is asymptomatic, stratified by the type of heart valve disease as follows: • aortic [including bicuspid] stenosis • aortic regurgitation • mitral stenosis • mitral regurgitation • tricuspid regurgitation Exclusion • Children (aged <18 years)
Prognostic variable	Left ventricular systolic function based on global longitudinal strain
Confounding factor	• Surgical risk scores (e.g. EuroScore I or II, STS) • Age • Sex • Renal impairment • Previous cardiac surgery • Diabetes • Hypertension • Prior MI • Frailty scores (e.g. CSHA, Katz score)
Outcome	• Mortality (≥12 months after surgery) • Hospital admission for heart failure (≥12 months after surgery)
Study design	Cohort Randomised controlled trial would provide the strongest evidence

Timeframe	Long term
Additional information	None

1

2