National Institute for Health and Care Excellence

Final

Heart valve disease presenting in adults: investigation and management

[B] Evidence review for indications for referral to a specialist following echocardiography

NICE guideline NG208

Evidence reviews underpinning recommendations 1.1.6 and 1.1.7 in the NICE guideline

November 2021

Final

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

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1.1 Review question

In adults with heart valve disease who have had echocardiography, what are the indications for referral to a specialist?

1.1.1 Introduction

Not all individuals having had a diagnosis of heart valve disease will need to be referred to a specialist following assessment with echocardiography. The prevalence of mild heart valve disease is high in asymptomatic individuals; for example, the OxValve study found mild heart valve disease in 44.4% of screened individuals over 65 years of age. The progression of heart valve disease to clinically significant levels (moderate to severe) is slow, developing over several years or even decades. To improve clinical pathways, it is important to define the indications for referral to a specialist of adults who have had echocardiography.

1.1.2 Summary of the protocol

For full details see the review protocol in Appendix A.

Table 1: PICO characteristics of review question

Population	Adults aged 18 years and over with diagnosed heart valve disease who have had echocardiography, 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 less than 18 years. • Adults with congenital heart disease (excluding bicuspid aortic valves). • Tricuspid stenosis and pulmonary valve disease. 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).
Indications for referral	• Severe valve disease (± symptoms) • Moderate valve disease + asymptomatic • Moderate valve disease + symptomatic *Severity assessed by echo and rated as per British Society of Echocardiography criteria. Symptom status from clinical assessment.*
Confounding factors	Key confounding factors:

	• Left ventricular ejection fraction • Left ventricular stroke volume index • Coexistent second heart valve disease • Co-existing coronary disease • Age • Frailty (e.g., CSHA, Katz score)
Outcomes	Need for referral based on: • Mortality (without intervention after follow-up ≥12 months) • NYHA class change by 2 classes (e.g. class II to class IV; or hospital admission for heart failure) (after follow-up ≥12 months) • Need for intervention 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.
Study design	• Prospective and retrospective cohort studies that control for confounders in the study design or analysis with multivariate analysis • Systematic reviews of the above • If no cohort studies are identified case control studies that control for confounders in the study design or analysis will be included but downgraded for risk of bias

1.1.3 Methods and process

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

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

1.1.4 Prognostic evidence

1.1.4.1 Included studies

A search was conducted for prospective or retrospective cohort studies investigating the prognostic value of the following factors compared to each other or another heart valve disease severity or symptom status: severe valve disease (± symptoms), moderate valve disease + asymptomatic and moderate valve disease + symptomatic, reporting outcomes of mortality (without intervention), New York Heart Association (NYHA) class change by 2 classes (e.g. class II to class IV; or hospital admission for heart failure) and/or need for intervention in people with diagnosed heart valve disease that have had echocardiography. The populations were stratified from the outset by type of valve disease (aortic stenosis, aortic regurgitation, mitral stenosis, mitral regurgitation and tricuspid regurgitation).

All studies conducted a multivariable analysis, but different variables were analysed in the studies (see Table 2). To be included, studies had to have performed some form of multivariate analysis. If studies had not included one or more of the variables that had been pre-specified in the protocol, studies were still included but downgraded further for confounding in the risk of bias assessment.

Eleven cohort studies (4 prospective and 7 retrospective) were included in the review;[10, 16, 35, 36, 40, 71, 92, 113, 121, 135, 137] these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summaries below (Table 3 to Table 18).

Of the different population strata listed in the protocol, the only one where no evidence was identified was mitral stenosis. Evidence was identified for all of the remaining strata, as follows:

- **Aortic stenosis (AS)** – 6 studies in total, some reporting more than one prognostic factor as detailed below:
    - Moderate AS:
        - symptomatic vs. asymptomatic/minimally symptomatic (2 studies);[10, 35]
    - Mild-moderate AS with or without symptoms:
        - moderate AS vs. mild AS (based on aortic valve area or mean gradient) (1 study);[71]
    - Mild-moderate asymptomatic AS:
        - moderate AS vs. mild AS (based on peak aortic jet velocity) (1 study);[121]
    - Mild-severe AS with or without symptoms:
        - severe AS vs. mild-moderate AS (based on aortic valve area or mean gradient) (1 study);[92]
    - Trivial-severe AS with or without symptoms:
        - low-gradient low-flow (LG/LF) severe AS vs. trivial-moderate AS (based on aortic valve area) (1 study);[137]
        - low-gradient normal-flow (LG/NF) severe AS vs. trivial-moderate AS (based on aortic valve area) (1 study);[137]
        - high gradient (HG) severe AS vs. trivial-moderate AS (based on aortic valve area) (1 study);[137]

  Pooling of any of the studies for aortic stenosis was not thought to be appropriate due to different populations (i.e. some including trivial-severe AS while others only including mild-severe or mild-moderate AS), different ways of defining severity (i.e. some basing severity on aortic valve area and others on mean gradient or peak aortic jet velocity) or different referents (comparators) (i.e. for the severe prognostic factor, some studies compare this to the trivial-moderate cases while others compare it mild-moderate cases, which could lead to different results).

- **Aortic regurgitation (AR)** – 1 study reporting two different prognostic factors, as detailed below:
    - Mild-severe asymptomatic AR:
        - severe AR vs. mild AR (based on quantitative American Society of Echocardiography thresholds) (1 study);[36]
        - moderate AR vs. mild AR (based on quantitative American Society of Echocardiography thresholds) (1 study);[36]

- **Mitral regurgitation (MR)** – 2 studies reporting 3 different prognostic factors, as detailed below:
    - Moderate-severe asymptomatic MR: severe MR vs moderate MR (based on regurgitant volume on echo) (1 study);[113]
    - Mild-severe asymptomatic MR:
        - severe MR vs. mild MR (based on effective regurgitant orifice) (1 study);[40]
        - moderate MR vs. mild MR (based on effective regurgitant orifice) (1 study);[40]

- **Tricuspid regurgitation (TR)** – 2 studies focused on functional TR, both reporting multiple different prognostic factors, as detailed below:
    - Trivial-severe functional symptomatic TR:
        - severe functional TR vs. trivial functional TR (based on American Society of Echocardiography guidelines) (1 study);[16]
        - moderate functional TR vs. trivial functional TR (based on American Society of Echocardiography guidelines) (1 study);[16]
    - Trivial-severe functional TR with or without symptoms:
        - severe functional TR vs. trivial-moderate functional TR (based on effective regurgitant orifice) (1 study);[135]

Pooling of the two studies looking at severe functional TR as a prognostic factor among a population of trivial-severe functional TR was not thought to be appropriate as the referents used in the two studies were different (i.e. in one study the outcome in the severe group was compared to trivial-moderate cases, while in the other study this was only compared to the trivial group, which could lead to different results). None of the studies reported on the outcome of NYHA class change.

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.

1.1.4.2 Excluded studies

See the excluded studies list in Appendix J

1.1.5 Summary of studies included in the prognostic evidence

Table 2: Summary of studies included in the evidence review

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
Aortic stenosis (AS)						
Bae 2020[10] Retrospective cohort N=148 Republic of Korea	**Moderate AS (peak aortic jet velocity between 3.0 and 4.0 m/s, mean transvalvular pressure gradient between 30 and 40 mmHg,** or aortic valve area between 1.0 and 1.5 cm2) Mean age: 69.3 (11.2) years	Multivariate Cox proportional hazards analysis	New York Heart Association (NYHA) class III-IV (symptomatic) Referent was NYHA class I-II (asymptomatic/minimally symptomatic)	Diabetes, AV area < 1.25 cm2, moderate or moderate-to-severe MR, LVEF, E/e', LVESD, IVRT, NT pro-BNP, creatinine, very high CV risk	Composite of CV death, AV replacement, and hospitalization for worsening heart failure Mean follow-up: 5.6 years	Risk of bias: very high Indirectness: Prognostic factor – prognostic groups are split into asymptomatic/minimally symptomatic and symptomatic groups based on NYHA classes of I-II and III-IV, respectively. Ideally would be interested in

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
	Retrospective review of patient records from echocardiography labs of a tertiary centre between 2008 and 2012					asymptomatic vs. any symptoms in line with the protocol. Outcome indirectness – composite of outcomes included in the protocol.
Delesalle 2019[35] Retrospective cohort N=508 France	**Moderate AS** (aortic valve area on echocardiography between 1.0 and 1.5 cm^2) Mean age: 75 (11) years Retrospective review of database enrolling patients from echocardiography labs of two French tertiary centres between 2000 and 2014	Multivariate Cox proportional hazards analysis	New York Heart Association (NYHA) class III-IV (symptomatic) Referent was NYHA class I-II (asymptomatic/minimally symptomatic)	Age, sex, body surface area, NYHA class, prior atrial fibrillation, mean transaortic pressure gradient, left ventricular ejection fraction, history of myocardial infarction, moderate-severe aortic valve calcification, Charlson comorbidity index and aortic valve replacement during follow-up were included in the multivariate model. Of those pre-specified in the protocol, only age and ejection fraction were included in the model.	All-cause mortality Medically managed initially as there was the option to perform surgery once progressed to severe AS – analysis is adjusted for valve replacement being performed during follow-up. Time-to-event data as Cox proportional hazards used for analysis Median (IQR) follow-up: 47 (24-80) months	Risk of bias: very high Indirectness: Prognostic factor – prognostic groups are split into asymptomatic/minimally symptomatic and symptomatic groups based on NYHA classes of I-II and III-IV, respectively. Ideally would be interested in asymptomatic vs. any symptoms in line with the protocol.
Kearney 2013[71]	**Mild or moderate AS** (aortic	Multivariate forward stepwise	Moderate AS (aortic valve area 1.0-1.5	Two different models reported.	Progression to severe	Risk of bias: very high

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
Prospective cohort N=132 (note: this refers to mild-moderate cases as severe cases were not relevant to the outcome that was extracted) Australia	valve area >1.0 cm^2 or mean aortic gradient ≤40 mmHg) Consecutive patients >60 years from single tertiary hospital in Australia between 1988 and 1994 Mean age 73 (6) years (including n=15 cases of severe AS that were not included in the analysis for the outcome extracted).	logistic regression analysis	cm^2 or mean gradient 25-40 mmHg) Referent was mild AS (aortic valve area >1.5 cm^2 or mean gradient <25 mmHg)	Although one had adjusted for one more variable than the other, both were extracted as data for the additional confounder was only 62% complete. List of confounders included in the models was not clear but was said to be all of those with P<0.05 on univariate analysis. Therefore, the following were assumed to be included: <u>Model 1:</u> duration of follow-up, history of myocardial infarction, baseline AS severity, mean aortic valve gradient and aortic valve calcification <u>Model 2:</u> duration of follow-up, history of myocardial infarction, baseline AS severity and mean aortic valve gradient	AS during follow-up Medically managed as follow-up was censored at time of aortic valve replacement or death Mean (SD) follow-up 6.5 (4.3) years	Indirectness: Prognostic factor – moderate valve disease with/without symptoms, whereas ideally aimed to look at moderate symptomatic and moderate symptomatic as separate prognostic factors Outcome – progression to severe disease not listed in protocol but included as indirect evidence for need for intervention. However, study defines indication for intervention as severe + symptomatic and no information on symptom status of these patient.

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
				Of those pre-specified in the protocol, none were included in the multivariate analysis.		
Malouf 2012[92] Retrospective cohort N=360 USA	**Mild-severe AS** (aortic valve area <2.0 cm^2 and mean gradient >10 mmHg) All patients with first diagnosis of native aortic stenosis entered into database between 1st January 1988 and 31st December 1997 from Olmsted Country community referred to Mayo clinic Mean age 74 (14) years	Cox proportional hazards analysis	Severe AS based on valve area (<1.0 cm^2) Referent was mild or moderate AS (aortic valve area ≥1.0 cm^2) Severe AS based on mean gradient (≥40 mmHg) Referent was mild or moderate AS (mean gradient <40 mmHg)	Variables included in model differed depending on outcome and prognostic factor. Some uncertainty as to full listed for each, but those clearly included have been listed below: <u>Severe AS based on valve area, mortality outcome</u>: valve area <1.0 cm^2, age, sex, comorbidity score and atrial fibrillation. Possibly also ejection fraction and class III-IV symptoms. <u>Severe AS based on valve area, congestive heart failure outcome:</u> valve area <1.0 cm^2, age, comorbidity score and atrial fibrillation. Possibly also	Mortality after diagnosis Congestive heart failure development Aortic valve replacement during follow-up Medically managed initially and censored at time of aortic valve replacement for mortality and congestive heart failure outcomes Mean (SD) follow-up: 7.5 (4.2) years	Risk of bias: very high for all outcomes and prognostic factor combinations Indirectness: None

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
				ejection fraction and class III-IV symptoms. Severe AS based on aortic valve area, for aortic valve replacement outcome: valve area <1.0 cm^2, age, sex, comorbidity score, atrial fibrillation, ejection fraction and class III-IV symptoms. Severe AS based on mean gradient for aortic valve replacement outcome: mean gradient ≥40 mmHg, age, sex, comorbidity score, atrial fibrillation, ejection fraction and class III-IV symptoms. Of those pre-specified in the protocol, only 1-2 (age and/or coronary disease or ejection fraction depending on prognostic factor/outcome) were included in the		

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
				multivariate analysis.		
Rosenhek 2004[121] Retrospective cohort study N=176 Austria	**Asymptomatic mild or moderate AS** (peak aortic jet velocity 2.5-3.9 m/s) Consecutive patients from single echocardiography laboratory between 1st January and 31st December Mean age 58 (19) years	Cox proportional hazards analysis	Moderate AS (peak aortic jet velocity ≥3 m/s) Referent was mild AS (peak aortic jet velocity <3 m/s)	The following variables were included in the model: age ≥50 years, gender, coronary artery disease, hypertension, diabetes, hypercholesterolaemia, aortic valve peak velocity ≥3 m/s and aortic valve calcification score 3 or 4. Of those pre-specified in the protocol, only age and coronary artery disease were included in the multivariate analysis.	Aortic valve replacement or death Medically managed initially as aortic valve replacement forms part of the outcome Median follow-up: 55 months (range, 1-76 months)	Risk of bias: very high Indirectness: None
Tribouilloy 2015[137] Retrospective cohort N=809 France	**Mild-severe AS** (aortic valve calcification with reduction in systolic movements and valve area <2 cm^2) Consecutive patients at two French echocardiography laboratorial between 2000 and 2012	Cox proportional hazards analysis	Low-gradient low-flow severe AS (aortic valve area <1 cm^2, indexed valve area <0.6 cm^2, mean gradient <40 mmHg and stroke volume index <35 ml/m^2) Low-gradient normal-flow severe AS (aortic valve area <1 cm^2, indexed valve area <0.6 cm^2, mean gradient <40 mmHg	The following variables were included in the model: severity classification, age, sex, body surface area, Charlson comorbidity index, symptoms at baseline, coronary artery disease, history of atrial fibrillation	All-cause mortality Medically managed and censored at time of cardiac surgery Median follow-up with medical management: 22.8 months (range, 7-53 months). Median overall	Risk of bias: very high for all prognostic factors Indirectness: Prognostic factor – severe AS split into different groups each compared with same referent rather than looking at severe as a whole, as

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
	Mean age 75 (12) years		and stroke volume index ≥35 ml/m^2) High-gradient severe AS (aortic valve area <1 cm^2, indexed valve area <0.6 cm^2, mean gradient ≥40 mmHg) Referent for all three prognostic factors was mild-moderate AS (aortic valve area ≥1.0 cm^2 or indexed valve area ≥0.6 cm^2 and mean gradient <40 mmHg)	and ejection fraction Of those pre-specified in the protocol, only age, ejection fraction and coronary disease were included in the multivariate analysis.	follow-up: 39.0 months (range, 11-69 months)	specified in protocol
Aortic regurgitation						
Detaint 2008[36] Prospective cohort N=251 USA	**Asymptomatic mild-severe aortic regurgitation** (AR; based on standard colour-flow imaging) Consecutive patients between 1991 and 2003. Likely to be single centre but unclear. Mean age 60 (17) years	Cox proportional hazards analysis	QASE-severe grade (regurgitant volume ≥60 ml/beat or effective regurgitant orifice area ≥30 mm^2) QASE-moderate grade (regurgitant volume ≥30 ml/beat or effective regurgitant orifice area ≥10 mm^2, but not reaching severe thresholds) Referent in both cases was QASE-mild grade (regurgitant volume <30	Variables included in multivariate models differed depending on the outcome: <u>Mortality:</u> age, gender, AR quantitative classification, comorbidity score and ejection fraction <u>Mortality or aortic valve replacement for AR:</u> age, gender, AR quantitative classification, end-systolic volume index and comorbidity index	Mortality Mortality or aortic valve replacement Medically managed Mean (SD) follow-up: 8 (3.8) years	Risk of bias: very high for all prognostic factor and outcome combinations Indirectness: None

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
			ml/beat and effective regurgitant orifice area <10 mm^2) QASE refers to the quantitative American Society of Echocardiography threshold, which were used for AR grading	Of those pre-specified in the protocol, only 1-2 (age alone or age and ejection fraction depending on outcome) were included in the multivariate analysis.		
Mitral regurgitation						
Enriquez-Sarano 2005[40] Prospective cohort N=456 USA	**Asymptomatic mild-severe mitral regurgitation** (MR; on colour-flow imaging) Mean age 63 (14) years Matching inclusion criteria between 1991 and 2000 at single centre (Mayo Clinic)	Cox proportional hazards analysis	Severe MR (effective regurgitant orifice area ≥40 mm^2) Moderate MR (effective regurgitant orifice area 20-39 mm^2) Referent for both prognostic factors was mild MR (effective regurgitant orifice area <20 mm^2)	The following variables were included in the multivariate analysis for both prognostic factors: effective regurgitant orifice threshold grouping, age, sex, ejection fraction, presence of diabetes and presence of atrial fibrillation Of those pre-specified in the protocol, only 2 (age and ejection fraction) were included in the multivariate analysis. Additionally, other valve disease was an exclusion criterion.	All-cause mortality Medically managed and censored at time of surgery Mean (SD) follow-up post-diagnosis was 2.7 (2.9) years under medical management and 5.1 (2.9) years under medical and surgical management	Risk of bias: very high for both prognostic factors Indirectness: None

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
Penicka 2018[113] N=258 Prospective cohort Belgium and Czech Republic	Asymptomatic, chronic moderate and severe organic MR attributable to flail or prolapse	Cox proportional hazards regression model	Echo-derived organic mitral regurgitation category: severe (regurgitant volume ≥60 ml) vs moderate (regurgitant volume 30-59 ml)	Age, sex, and LVESD on echo.	All-cause mortality Indication for mitral valve surgery Median (IQR)follow-up 5.0 (3.5-6.0) years	Risk of bias: very high Indirectness: None identified
Tricuspid regurgitation						
Benfari 2019[16] Retrospective cohort N=11,507 USA	**Heart failure with reduced ejection fraction and trivial-severe functional tricuspid regurgitation** (TR; according to American Society of Echocardiography guidelines) Patients from single clinic (Mayo Clinic) diagnosed between 2003 and 2011 Mean age 68 (14) years	Cox proportional hazards analysis	Severe functional TR (graded according to American Society of Echocardiography guidelines) Moderate functional TR (graded according to American Society of Echocardiography guidelines) Referent for both prognostic factors was trivial functional TR (graded according to American Society of Echocardiography guidelines)	The two models that had adjusted for the most variables were extracted and are detailed below: Model 1: age, sex, ejection fraction, atrial fibrillation, E/e′, pulmonary hypertension, Charlson comorbidity index and MAGGIC score Model 2: age, sex, ejection fraction, atrial fibrillation, E/e′, pulmonary hypertension, Charlson comorbidity index and right ventricular dysfunction degree	Mortality Under medical management Median (IQR) follow-up: 4.02 (0.95-7.12) years	Risk of bias: high for all prognostic factor and model combinations Indirectness: For moderate functional TR as prognostic factor – asymptomatic and symptomatic combined, whereas ideally aimed to look at asymptomatic and symptomatic moderate disease as separate prognostic factors

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
				Of those pre-specified in the protocol, only 2 (age and ejection fraction) were included in the multivariate analysis. Others may have been captured in one of the risk scores included.		
Topilsky 2018[135] Retrospective cohort N=291 Israel and USA	**Trivial-severe functional TR due to systolic left ventricular dysfunction** (graded according to echocardiography measurements of effective regurgitant orifice area) Mean age 70.0 (11.5) years Consecutive mild-severe patients between 1995 and 2005 were included, and a random group of patients from those with trivial	Cox proportional hazards analysis	Severe functional TR (effective regurgitant orifice area ≥0.4 cm^2) Referent was trivial, mild or moderate functional TR (effective regurgitant orifice area <0.4 cm^2)	The model that had adjusted for the most variables was extracted and included in the results. The following variables were included: effective regurgitant orifice area ≥0.4 cm^2, age, sex, comorbidity index, left ventricular ejection fraction, atrial fibrillation, left atrial size, right ventricular dysfunction ≥moderate, renal failure and right ventricular systolic pressure. Of those pre-specified in	All-cause mortality Medically managed and censored at time of surgery Median follow-up (unclear if range or IQR): 1.9 (0.5-6.6) years	Risk of bias: very high Indirectness: None

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
	TR and similar eligibility criteria were included from a database. Unclear whether single site or multiple.			the protocol, only 2 (age and ejection fraction) were included in the multivariate analysis. Others may have been captured in the risk score included.		

See Appendix D for full evidence tables.

1.1.6 Summary of the prognostic evidence

Aortic stenosis

Table 3: Clinical evidence summary: symptomatic (NYHA class III or IV) versus asymptomatic moderate AS

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Risk of bias	Imprecision	Indirectness	GRADE Quality
Symptomatic (NYHA class III or IV) vs. asymptomatic/ minimally symptomatic (NYHA class I-II) for predicting **all-cause mortality** Follow up: median 47 months (moderate AS; mean age: 75 (11) years; medically managed initially and adjusted for aortic valve replacement in	1 (n=508)	Adjusted HR 1.04 (0.89 to 1.21)[a]	Very serious[b]	Serious[c]	Serious[d]	VERY LOW

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Risk of bias	Imprecision	Indirectness	GRADE Quality
analysis if performed)						
Symptomatic (NYHA class III or IV) vs. asymptomatic/ minimally symptomatic (NYHA class I-II) for predicting **CV death, AV replacement, and hospitalisation for worsening HF** Follow up: mean 5.6 years (moderate AS)		Adjusted HR 3.84 (1.72 to 8.56)[e]	Very serious[b]	None	Serious[d]	VERY LOW

(a) Methods: multivariable analysis, including some but not all variables pre-specified in the protocol. The following variables were included: age, sex, body surface area, New York Heart Association class, prior atrial fibrillation, mean transaortic pressure gradient, left ventricular ejection fraction, history of myocardial infarction, moderate-severe aortic valve calcification, Charlson comorbidity index and aortic valve replacement

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

(c) 95% CIs cross null line

(d) Prognostic factor indirectness - prognostic groups are split into asymptomatic/minimally symptomatic and symptomatic groups based on NYHA classes of I-II and III-IV, respectively. Ideally would be interested in asymptomatic vs. any symptoms in line with the protocol.

(e) Methods: multivariable analysis, including some but not all variables prespecified in the protocol. The following variables were included: Diabetes, AV area < 1.25 cm2, moderate or moderate-to-severe MR, LVEF, E/e', LVESD, IVRT, NT pro-BNP, creatinine, very high CV risk

Table 4: Clinical evidence summary: moderate versus mild AS with or without symptoms

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Risk of bias	Imprecision	Indirectness	GRADE Quality
Moderate AS (aortic valve area 1.0-1.5 cm^2 or mean gradient 25-40 mmHg) vs. mild AS (aortic valve area >1.5 cm^2 or mean gradient <25 mmHg) for predicting **progression to severe AS during follow-up** Follow up: mean 6.5 years	1 (n=132)	<u>Model 1:</u> Adjusted OR 5.72 (1.47 to 22.3)[b] <u>Model 2:</u> Adjusted OR 10.5 (3.76 to 29.32)[c]	Very serious[d]	None	Very serious[e]	VERY LOW

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Risk of bias	Imprecision	Indirectness	GRADE Quality
(mild-moderate AS; mean age 73 (6) years[a]; medically managed initially and follow-up censored at time of aortic valve replacement or death)						

(a) Note: this mean age includes n=15 patients with severe AS that were not included in the analysis extracted, as a separate mean age for the mild-moderate population was not provided.

(b) Methods: multivariable analysis, not including any of those pre-specified in the protocol. The following variables were included: duration of follow-up, history of myocardial infarction, mean aortic valve gradient and aortic valve calcification (note only 62% had complete data for this variable).

(c) Methods: multivariable analysis, not including any of those pre-specified in the protocol. The following variables were included: duration of follow-up, history of myocardial infarction and mean aortic valve gradient.

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

(e) Prognostic factor indirectness: moderate severity valve disease with/without symptoms used as prognostic factor, whereas ideally the aim was to look at moderate symptomatic and moderate asymptomatic valve disease as separate prognostic factors; outcome indirectness: progression to severe valve disease is not listed as an outcome in the protocol but has been included as indirect evidence for need for intervention due to limited other available evidence. However, the study defines indication for intervention as severe + symptomatic and is therefore indirect as there is no information as to the symptomatic status of patients and therefore the requirement for intervention.

Table 5: Clinical evidence summary: moderate versus mild asymptomatic AS

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Risk of bias	Imprecision	Indirectness	GRADE Quality
Moderate asymptomatic AS (peak aortic jet velocity ≥3 m/s) vs. mild asymptomatic AS (peak aortic jet velocity <3 m/s) for predicting **aortic valve replacement or death** Follow up: median 55 months (asymptomatic mild-moderate AS; mean age 58 (19) years; medically managed initially as aortic valve replacement forms part of the outcome)	1 (n=176)	Adjusted HR 1.6 (1.04 to 2.80)[a]	Very serious[b]	None	None	LOW

(a) Methods: multivariable analysis, including some but not all variables pre-specified in the protocol. The following variables were included: age ≥50 years, gender, coronary artery disease, hypertension, diabetes, hypercholesterolaemia, aortic valve peak velocity ≥3 m/s (moderate) and aortic valve calcification score 3 or 4. Result listed as RR in study table but methods state Cox proportional hazards used, so reported as HR here.

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

Table 6: Clinical evidence summary: severe versus mild-moderate AS with or without symptoms

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Risk of bias	Imprecision	Indirectness	GRADE Quality
Severe AS based on valve area (<1.0 cm^2) vs. mild-moderate AS (aortic valve area ≥1.0 cm^2) for predicting **mortality** Follow up: mean 7.5 years (mild-severe AS; mean age 74 (14) years for whole study – mean age for prognostic factor and referent groups was 77.0 and 72.3 years, respectively; medically managed initially and censored at time of aortic valve replacement)	1 (n=360)	Adjusted HR 1.81 (1.19 to 2.75)[a]	Very serious[b]	None	None	LOW
Severe AS based on valve area (<1.0 cm^2) vs. mild-moderate AS (aortic valve area ≥1.0 cm^2) for predicting **congestive heart failure** Follow up: mean 7.5 years (mild-severe AS; mean age 74 (14) years for whole study – mean age for prognostic factor and referent groups was 77.0 and 72.3 years, respectively; medically managed initially and censored at time of aortic valve replacement)	1 (n=360)	Adjusted HR 2.3 (1.3 to 4.07)[c]	Very serious[b]	None	None	LOW
Severe AS based on valve area (<1.0 cm^2) vs. mild-moderate AS (aortic valve area ≥1.0 cm^2) for predicting **aortic valve replacement during follow-up** Follow up: mean 7.5 years (mild-severe AS; mean age 74 (14) years for whole study – mean age for prognostic factor and referent groups was 77.0 and 72.3 years, respectively; medically managed initially)	1 (n=360)	Adjusted HR 2.8 (1.6 to 4.9)[d]	Very serious[b]	None	None	LOW

(a) Methods: multivariable analysis, including some but not all variables pre-specified in the protocol. The following variables were included: valve area <1.0 cm^2, age, sex, comorbidity score and atrial fibrillation. Possibly also included ejection fraction and class III-IV symptoms, but unclear. May have been others included but not well reported.

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

(c) Methods: multivariable analysis, including some but not all variables pre-specified in the protocol. The following variables were included: valve area <1.0 cm^2, age, comorbidity score and atrial fibrillation. Possibly also included ejection fraction and class III-IV symptoms, but unclear. May have been others included but not well reported.

(d) Methods: multivariable analysis, including some but not all variables pre-specified in the protocol. The following variables were included: valve area <1.0 cm^2, age, sex, comorbidity score, atrial fibrillation, ejection fraction and class III-IV symptoms. May have been others included but not well reported.

Table 7: Clinical evidence summary: severe versus mild-moderate AS with or without symptoms

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Risk of bias	Imprecision	Indirectness	GRADE Quality
Severe AS based on mean gradient (≥40 mmHg) vs. mild-moderate AS (mean gradient <40 mmHg) for predicting **aortic valve replacement during follow-up** Follow up: mean 7.5 years (mild-severe AS; mean age 74 (14) years for whole cohort; medically managed initially)	1 (n=360)	Adjusted HR 5.8 (3 to 11.21)[a]	Very serious[b]	None	None	LOW

(a) Methods: multivariable analysis, including some but not all variables pre-specified in the protocol. The following variables were included: mean gradient ≥40 mmHg, age, sex, comorbidity score, atrial fibrillation, ejection fraction and class III-IV symptoms. May have been others included but not well reported.

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

Table 8: Clinical evidence summary: low-gradient low-flow severe AS versus mild-moderate AS with or without symptoms

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Risk of bias	Imprecision	Indirectness	GRADE Quality
Low-gradient low-flow severe AS (aortic valve area <1 cm^2, indexed valve area <0.6 cm^2, mean gradient <40 mmHg and stroke volume index <35 ml/m^2 vs. mild-moderate AS (aortic valve area ≥1.0 cm^2 or indexed valve area ≥0.6 cm^2 and mean gradient <40 mmHg) for predicting **all-cause mortality** Follow up: median 22.8 months.	1 (n=477)	Adjusted HR 0.88 (0.53 to 1.46)[a]	Very serious[b]	Serious[c]	Serious[d]	VERY LOW

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Risk of bias	Imprecision	Indirectness	GRADE Quality
(mild-severe AS; mean age 75 (12) years for whole study – median age for the prognostic factor and referent groups was 78.5 and 76.9 years, respectively; medically managed initially and censored at time of cardiac surgery)						

(a) Methods: multivariable analysis, including some but not all variables pre-specified in the protocol. The following variables were included: severity classification, age, sex body surface area, Charlson comorbidity index, symptoms at baseline, coronary artery disease, history of atrial fibrillation and ejection fraction.

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

(c) 95% CIs cross null line

(d) Prognostic factor indirectness - severe AS is split into three different groups that are each compared with the same referent of mild-moderate AS, rather than looking at severe AS as a whole as a prognostic factor as specified in the protocol.

Table 9: Clinical evidence summary: low-gradient normal-flow severe AS versus mild-moderate AS with or without symptoms

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Risk of bias	Imprecision	Indirectness	GRADE Quality
Low-gradient normal-flow severe AS (aortic valve area <1 cm^2, indexed valve area <0.6 cm^2, mean gradient <40 mmHg and stroke volume index ≥35 ml/m^2) vs. mild-moderate AS (aortic valve area ≥1.0 cm^2 or indexed valve area ≥0.6 cm^2 and mean gradient <40 mmHg) for predicting **all-cause mortality** Follow up: median 22.8 months (mild-severe AS; mean age 75 (12) years for whole study – median age for the prognostic factor and referent groups was 79.3 and 76.9 years, respectively; medically managed initially and censored at time of cardiac surgery)	1 (n=505)	Adjusted HR 1.06 (0.66 to 1.71)[a]	Very serious[b]	Serious[c]	Serious[d]	VERY LOW

(a) Methods: multivariable analysis, including some but not all variables pre-specified in the protocol. The following variables were included: severity classification, age, sex, body surface area, Charlson comorbidity index, symptoms at baseline, coronary artery disease, history of atrial fibrillation and ejection fraction.

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

(c) 95% CIs cross null line

(d) Prognostic factor indirectness - severe AS is split into three different groups that are each compared with the same referent of mild-moderate AS, rather than looking at severe AS as a whole as a prognostic factor as specified in the protocol.

Table 10: Clinical evidence summary: high-gradient severe AS versus mild-moderate AS with or without symptoms

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Risk of bias	Imprecision	Indirectness	GRADE Quality
High-gradient severe AS (aortic valve area <1 cm^2, indexed valve area <0.6 cm^2, mean gradient ≥40 mmHg) vs. mild-moderate AS (aortic valve area ≥1.0 cm^2 or indexed valve area ≥0.6 cm^2 and mean gradient <40 mmHg) for predicting **all-cause mortality** Follow up: median 22.8 months (mild-severe AS; mean age 75 (12) years for whole study – median age for the prognostic factor and referent groups was 76.9 and 76.9 years, respectively; medically managed initially and censored at time of cardiac surgery)	1 (n=667)	Adjusted HR 1.47 (1.03 to 2.1)[a]	Very serious[b]	None	Serious[c]	VERY LOW

(a) Methods: multivariable analysis, including some but not all variables pre-specified in the protocol. The following variables were included: severity classification, age, sex, body surface area, Charlson comorbidity index, symptoms at baseline, coronary artery disease, history of atrial fibrillation and ejection fraction.

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

(c) Prognostic factor indirectness - severe AS is split into three different groups that are each compared with the same referent of mild-moderate AS, rather than looking at severe AS as a whole as a prognostic factor as specified in the protocol.

Aortic regurgitation

Table 11: Clinical evidence summary: QASE-severe versus moderate grade asymptomatic AR

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Risk of bias	Imprecision	Indirectness	GRADE Quality
QASE[a]-severe grade (regurgitant volume ≥60 ml/beat or effective regurgitant orifice area ≥30 mm^2) vs. QASE[a]-mild grade (regurgitant volume <30 ml/beat and effective regurgitant orifice	1 (n=144)	Adjusted HR 4.1 (1.4 to 12.01)[b]	Very serious[c]	None	None	LOW

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Risk of bias	Imprecision	Indirectness	GRADE Quality
area <10 mm^2) for predicting **mortality** Follow-up: mean 8.0 years. (asymptomatic mild-severe AR; mean age 60 (17) years for whole cohort – mean age for prognostic factor and referent groups was 58 and 62 years, respectively; medically managed initially)						
QASE[a]-severe grade (regurgitant volume ≥60 ml/beat or effective regurgitant orifice area ≥30 mm^2) vs. QASE[a]-mild grade (regurgitant volume <30 ml/beat and effective regurgitant orifice area <10 mm^2) for predicting **mortality or aortic valve replacement for AR** Follow-up: mean 8.0 years. (asymptomatic mild-severe AR; mean age 60 (17) years for whole cohort – mean age for prognostic factor and referent groups was 58 and 62 years, respectively; medically managed initially)	1 (n=144)	Adjusted HR 12.9 (5.4 to 30.82)[d]	Very serious[c]	None	None	LOW

(a) QASE refers to the quantitative American Society of Echocardiography thresholds, which were used for AR grading
(b) Methods: multivariable analysis, including some but not all variables pre-specified in the protocol. The following variables were included: age, gender, AR quantitative classification, comorbidity score and ejection fraction.
(c) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
(d) Methods: multivariable analysis, including some but not all variables pre-specified in the protocol. The following variables were included: age, gender, AR quantitative classification, end-systolic volume index and comorbidity index.

Table 12: Clinical evidence summary: QASE-moderate versus mild grade asymptomatic AR

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Risk of bias	Imprecision	Indirectness	GRADE Quality
QASE[a]-moderate grade (regurgitant volume ≥30 ml/beat or effective regurgitant orifice area ≥10 mm^2, but not reaching severe thresholds) vs. QASE[a]-	1 (n=158)	Adjusted HR 2.1 (0.8 to 5.51)[b]	Very serious[c]	Serious[d]	None	VERY LOW

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Risk of bias	Imprecision	Indirectness	GRADE Quality
mild grade (regurgitant volume <30 ml/beat and effective regurgitant orifice area <10 mm^2) for predicting **mortality** Follow-up: mean 8.0 years. (asymptomatic mild-severe AR; mean age 60 (17) years for whole cohort – mean age for prognostic factor and referent groups was 62 and 62 years, respectively; medically managed initially)						
QASE[a]-moderate grade (regurgitant volume ≥30 ml/beat or effective regurgitant orifice area ≥10 mm^2, but not reaching severe thresholds) vs. QASE[a]-mild grade (regurgitant volume <30 ml/beat and effective regurgitant orifice area <10 mm^2) for predicting **mortality or aortic valve replacement for AR** Follow-up: mean 8.0 years. (asymptomatic mild-severe AR; mean age 60 (17) years for whole cohort – mean age for prognostic factor and referent groups was 62 and 62 years, respectively; medically managed initially)	1 (n=158)	Adjusted HR 4 (1.7 to 9.41)[e]	Very serious[c]	None	None	LOW

(a) QASE refers to the quantitative American Society of Echocardiography thresholds, which were used for AR grading
(b) Methods: multivariable analysis, including some but not all variables pre-specified in the protocol. The following variables were included: age, gender, AR quantitative classification, comorbidity score and ejection fraction.
(c) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
(d) 95% CIs cross null line
(e) Methods: multivariable analysis, including some but not all variables pre-specified in the protocol. The following variables were included: age, gender, AR quantitative classification, end-systolic volume index and comorbidity index.

Mitral regurgitation

Table 13: Clinical evidence summary: severe versus moderate asymptomatic MR

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Risk of bias	Imprecision	Indirectness	GRADE Quality
Severe asymptomatic MR vs. moderate asymptomatic MR for predicting **all-cause mortality** Follow-up: median 5 years (asymptomatic moderate-severe MR)	1 (n=258)	Adjusted HR 1.21 (1 to 1.46)[a]	Very serious[b]	serious[c]	None	VERY LOW
Severe asymptomatic MR vs. moderate asymptomatic MR for predicting mitral valve surgery Follow-up: median 5 years (asymptomatic moderate-severe MR)	1 (n=258)	Adjusted HR 1.5 (1.32 to 1.7)[a]	Very serious[b]	None	None	LOW

(a) Methods: multivariable analysis, including some but not all variables pre-specified in the protocol. The following variables were included: Age, sex, and LVESD on echo.

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

(c) 95% CI crosses the null line

Table 14: Clinical evidence summary: severe versus mild asymptomatic MR

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Risk of bias	Imprecision	Indirectness	GRADE Quality
Severe asymptomatic MR (effective regurgitant orifice area ≥40 mm^2) vs. mild asymptomatic MR (effective regurgitant orifice area <20 mm^2) for predicting **all-cause mortality** Follow-up: mean 2.7 years. (asymptomatic mild-severe MR; mean age 63 (14) years for whole cohort – mean age of prognostic factor and referent groups was 61 and 64 years, respectively;	1 (n=327)	Adjusted HR 2.9 (1.33 to 6.32)[a]	Very serious[b]	None	None	LOW

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

(a) Methods: multivariable analysis, including some but not all variables pre-specified in the protocol. The following variables were included: effective regurgitant orifice threshold grouping, age, sex, ejection fraction, presence of diabetes and presence of atrial fibrillation.

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

Table 15: Clinical evidence summary: moderate versus mild asymptomatic MR

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Risk of bias	Imprecision	Indirectness	GRADE Quality
Moderate asymptomatic MR (effective regurgitant orifice area 20-39 mm^2) vs. mild asymptomatic MR (effective regurgitant orifice area <20 mm^2) for predicting **all-cause mortality** Follow-up: mean 2.7 years. (asymptomatic mild-severe MR; mean age 63 (14) years for whole cohort – mean age of prognostic factor and referent groups was 65 and 64 years, respectively; medically managed initially and censored at time of surgery)	1 (n=258)	Adjusted HR 2.58 (1.25 to 5.32)[a]	Very serious[b]	None	None	LOW

(a) Methods: multivariable analysis, including some but not all variables pre-specified in the protocol. The following variables were included: effective regurgitant orifice threshold grouping, age, sex, ejection fraction, presence of diabetes and presence of atrial fibrillation.

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

Tricuspid regurgitation

Table 16: Clinical evidence summary: severe versus trivial functional symptomatic TR

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Risk of bias	Imprecision	Indirectness	GRADE Quality
Severe functional TR (graded according to American Society of Echocardiography guidelines) vs. trivial functional TR (graded according to American Society of	1 (n=5074)	Model 1: Adjusted HR 1.35 (1.11 to 1.64)[a] Model 2:	Serious[c]	None	None	MODERATE

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Risk of bias	Imprecision	Indirectness	GRADE Quality
Echocardiography guidelines) for predicting **mortality** Follow-up: median 4.02 years. (heart failure with reduced ejection fraction and trivial-severe functional TR; mean age 68 (14) years for whole cohort – mean age for prognostic factor and referent groups was 72 and 65 years, respectively; medically managed)		Adjusted HR 1.41 (1.25 to 1.59)[b]				

(a) Methods: multivariable analysis, including some but not all variables pre-specified in the protocol. The following variables were included: age, sex, degree of functional TR, ejection fraction, atrial fibrillation, E/e', pulmonary hypertension, Charlson comorbidity index and MAGGIC score

(b) Methods: multivariable analysis, including some but not all variables pre-specified in the protocol. The following variables were included: age, sex, degree of functional TR, ejection fraction, atrial fibrillation, E/e', pulmonary hypertension, Charlson comorbidity index and right ventricular dysfunction degree.

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

Table 17: Clinical evidence summary: moderate versus trivial functional symptomatic TR

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Risk of bias	Imprecision	Indirectness	GRADE Quality
Moderate functional TR (graded according to American Society of Echocardiography guidelines) vs. trivial functional TR (graded according to American Society of Echocardiography guidelines) for predicting **mortality** Follow-up: median 4.02 years. (heart failure with reduced ejection fraction and trivial-severe functional TR; mean age 68 (14) years for whole cohort – mean age for prognostic factor and referent groups was 71 and 65 years, respectively; medically managed)	1 (n=6 584)	<u>Model 1:</u> Adjusted HR 1.14 (1.01 to 1.29)[a] <u>Model 2:</u> Adjusted HR 1.17 (1.07 to 1.28)[b]	Serious[c]	None	Serious[d]	LOW

(a) Methods: multivariate analysis, including some but not all variables pre-specified in the protocol. The following variables were included: age, sex, degree of functional TR, ejection fraction, atrial fibrillation, E/e', pulmonary hypertension, Charlson comorbidity index and MAGGIC score

(b) Methods: multivariate analysis, including some but not all variables pre-specified in the protocol. The following variables were included: age, sex, degree of functional TR, ejection fraction, atrial fibrillation, E/e', pulmonary hypertension, Charlson comorbidity index and right ventricular dysfunction degree
(c) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
(d) Prognostic factor indirectness - includes moderate severity tricuspid regurgitation with or without symptoms, whereas in protocol ideally aimed to look at moderate + symptomatic and moderate + asymptomatic as separate prognostic factors

Table 18: Clinical evidence summary: severe versus trivial, mild or moderate functional TR with or without symptoms

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Risk of bias	Imprecision	Indirectness	GRADE Quality
Severe functional TR (effective regurgitant orifice area ≥0.4 cm^2) vs. trivial, mild or moderate functional TR (effective regurgitant orifice area <0.4 cm^2) for predicting **all-cause mortality** Follow-up: median 1.9 years. (trivial-severe functional TR due to systolic left ventricular dysfunction; mean age 70.0 (11.5) years for whole cohort – mean age for prognostic factor and referent groups was 69.3 and 70.1 years, respectively; medically managed and censored at time of surgery)	1 (n=291)	Adjusted HR 1.8 (1.16 to 2.8)[a]	Very serious[b]	None	None	LOW

(a) Methods: multivariable analysis, including some but not all variables pre-specified in the protocol. The following variables were included: effective regurgitant orifice ≥0.4 cm^2, age, sex, comorbidity index, left ventricular ejection fraction, atrial fibrillation, left atrial size, right ventricular dysfunction ≥moderate, renal failure and right ventricular systolic pressure.
(b) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

See Appendix F for full GRADE tables.

1.1.7 Economic evidence

1.1.7.1 Included studies

No health economic studies were included.

1.1.7.2 Excluded studies

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

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

1.1.9 Economic model

1.1.10 Unit costs

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

Resource	Unit costs	Source
Cardiology, outpatient, first visit	£172	NHS Reference Costs 2018-2019[107]

(a) NHS currency code WF01B

1.1.11 Evidence statements

Effectiveness

See the summary of evidence in Table 3, Table 4, Table 5, Table 6, Table 7, Table 8, Table 9, Table 10, Table 11, Table 12, Table 14, Table 15, Table 13, Table 16, Table 17, and Table 18.

Economic

- No relevant economic evaluations were identified.

1.1.12 The committee's discussion and interpretation of the evidence

1.1.12.1. The outcomes that matter most

All three outcomes listed in the protocol were primary outcomes and included mortality (without intervention), NYHA class change by two classes (e.g. class II to class IV) or hospitalisation for heart failure, and need for intervention, during follow-up.

For the mortality and NYHA class change/heart failure hospitalisation outcomes, an ideal follow-up length of ≥12 months was specified, though this was not used to exclude studies.

The included evidence covered various types and presentations of valve disease, which were analysed as separate populations from the outset of the review. The number of outcomes reported differs according to the type of valve disease and also the risk factor. However, in general, mortality was the outcome that was most reported across the studies, followed by need for intervention and NYHA class change/heart failure hospitalisation heart. Eight of the nine studies reported results for mortality, while only three and one study provided data for need for intervention and congestive heart failure, respectively.

1.1.12.2 The quality of the evidence

Strata and risk factors covered

No evidence was identified for the mitral stenosis population stratum. Some evidence was identified for all other types of heart valve disease strata listed in the protocol, though the prognostic factors covered and their definitions differed between the studies. For example, for some strata there was only information available for moderate valve disease while others reported data for both severe and moderate valve disease as prognostic factors.

Separate information on the prognostic effect of moderate valve disease with symptoms and without symptoms is lacking as most studies include symptomatic and asymptomatic moderate valve disease combined as the prognostic factor or assess the effect of moderate

valve disease in an entirely asymptomatic population, which does not give insight into how the effect of symptom status in moderate valve disease may alter its prognostic effect.

Quality and limitations

The quality of the evidence ranged from moderate to very low, with the majority being low or very low. The main reason for downgrading in all studies was risk of bias, though indirectness relative to the protocol was also an issue for many studies. Within the risk of bias rating, the most common reasons for downgrading were: limited reporting of patient characteristics, particularly those prespecified as confounders in the protocol; confounding adjustment – though all studies had to have performed some multivariate analysis to be included, in most cases only some and not all of the six prespecified confounders in the protocol were included in this analysis; and in some studies, there were fewer than 10 events per covariate in the analysis, making the estimates less reliable.

For some studies, indirectness relative to the protocol was also a reason for downgrading. In most cases this was due to prognostic factor indirectness. For example, in some cases studies reported the prognostic effect of moderate valve disease, the definition of which included symptomatic and asymptomatic moderate valve disease, whereas ideally the aim was to assess the prognostic effect of symptomatic moderate and asymptomatic moderate valve disease separately. Similarly, one study reported data for severe valve disease as a prognostic factor but split severe into three separate subgroups rather than providing data for severe valve disease overall.

There was only one study where outcome indirectness was considered to be present, which was because progression to severe disease was included as an indirect measure of need for intervention, which may not have been the case in all patients in the study if they were asymptomatic, as severe symptomatic valve disease was used as the indication for intervention in this study.

Although some studies reported similar risk factors in similar populations, no pooling was performed as there were differences between the studies in terms of the population covered (e.g. some included mild-severe disease while others include only mild-moderate disease) definitions used for the risk factor and the components of the composite outcome reported (e.g. some reported mortality only and others a composite of mortality and need for intervention).

Imprecision was a further reason for downgrading in some cases, but for most of the reported outcomes this was not observed.

Information about how the quality of the evidence was taken into account when making recommendations is included in the benefits and harms section below.

1.1.12.3 Benefits and harms

Symptom status in moderate AS

One study investigated the effect of being in NYHA class III or IV compared to NYHA class I or II on the outcome of all-cause mortality in a population with moderate AS that were medically managed, with adjustment for aortic valve replacement if performed during follow-up. The results suggest only slightly increased events in those in class III or IV compared to those in class I or II based on the point estimate, which was very close to the null line; however, the confidence intervals crossed the null line, meaning this was not a significant predictor of outcome, and the evidence was graded very low quality. One further study investigated the effect of being in NYHA class III or IV compared to NYHA class I or II on the outcome of CV death, AV replacement, and hospitalization for worsening heart failure and demonstrated this to be a significant predictor of outcome. Although an increased risk of this outcome was shown in the symptomatic group, because the outcome was indirect, the

quality of the evidence was very low and the finding conflicts with the other study, the committee did not find this evidence to be sufficient to inform any specific recommendations based on symptom status in moderate heart valve disease. However, recommendations that were made include people with moderate valve disease regardless of symptom status, so these populations are covered by recommendations.

Moderate AS

Two different studies investigated the prognostic effect of moderate compared to mild AS in a population consisting of mild or moderate AS patients. In one study there was a mixture of asymptomatic and symptomatic patients and the other study included only asymptomatic patients.

One study defined moderate AS as valve area 1.0-1.5 cm² or mean gradient 25-40 mmHg and the results from two separate models suggested that moderate AS is associated with increased progression to severe disease during follow-up compared to those with mild AS , with no imprecision identified and the evidence being graded very low quality. The outcome reported in this study was used as indirect evidence for need for intervention; however, progression to severe disease may not have indicated need for intervention in all cases, as symptomatic severe AS was reported to be the indication for intervention and it was unclear how many of those that progressed to severe AS were asymptomatic at the time of progression. Prognostic factor indirectness was also present as the study combines symptomatic and asymptomatic moderate AS as a single prognostic factor rather than looking individually at symptomatic moderate and asymptomatic moderate AS as prognostic factors.

The second study defined moderate AS as peak aortic jet velocity ≥3 m/s, with the results demonstrating that moderate AS does appear to be associated with increased death or aortic valve replacement compared to mild AS in those that are asymptomatic. Though the lower confidence interval comes close to 1.00, no imprecision was present as it did not cross 1.00. Evidence from this study was graded low quality.

Severe AS

Two separate studies report data for severe AS compared to mild-moderate AS, with each using different definitions of severe AS and reporting slightly different outcomes.

One study reported data for severe AS if defined using valve area <1.0 cm² and also if severe AS is defined as a mean gradient ≥40 mmHg on echocardiography. For the results when valve area was used to classify the severity of valve disease, severe AS was demonstrated to be associated with increased mortality , congestive heart failure and aortic valve replacement during follow-up, reported separately rather than as a composite outcome, compared to mild-moderate AS and evidence was graded low quality. When the same study used a mean gradient ≥40 mmHg as the definition of severe AS, severe AS was again associated with increased aortic valve replacement during follow-up compared to mild-moderate AS based on mean gradient, but the study did not report mortality or congestive heart failure for this prognostic factor. Evidence was graded low quality for this prognostic factor.

The second study defined severe AS as valve area <1.0 cm² but separated severe AS further into low-gradient low-flow severe AS (aortic valve area <1 cm^2, indexed valve area <0.6 cm^2, mean gradient <40 mmHg and stroke volume index <35 ml/m^2), low-gradient normal-flow severe AS (aortic valve area <1 cm^2, indexed valve area <0.6 cm^2, mean gradient <40 mmHg and stroke volume index ≥35 ml/m^2) and high-gradient severe AS (aortic valve area <1 cm^2, indexed valve area <0.6 cm^2, mean gradient ≥40 mmHg), with each being compared

to mild-moderate AS (aortic valve area ≥1.0 cm^2 or indexed valve area ≥0.6 cm^2 and mean gradient <40 mmHg). The results demonstrated that low-gradient low-flow severe and low-gradient normal-flow severe AS were not significant predictors for the outcome of all-cause mortality, as confidence intervals crossed the null line, while high-gradient severe AS was demonstrated to be a predictor of all-cause mortality compared to mild-moderate AS, which was significant as there was no imprecision identified despite the lower confidence interval coming close to 1.0. Evidence for all three severe subgroups was graded very low quality.

Overall, the two studies suggest that at least some presentations of severe AS are associated with worse outcome compared to those with mild-moderate AS, though the size of this effect may differ depending on which measure of severity is used, and one study demonstrated that severe AS was not a predictor of outcome when the specific subgroups of low-gradient low-flow severe AS and low-gradient normal-flow severe AS were considered.

Severe AR

One study reported data for the prognostic effect of severe AR, graded according to quantitative American Society of Echocardiography thresholds, compared to mild AR in terms of mortality alone and a composite outcome consisting of mortality and aortic valve replacement for AR in an asymptomatic population.

The results demonstrated that severe AR is associated with increased mortality (and mortality or aortic valve replacement for AR compared to those with mild AR, with no imprecision identified and the evidence being graded low quality.

Moderate AR

One study reported data for the prognostic effect of moderate AR, graded according to quantitative American Society of Echocardiography thresholds, compared to mild AR in terms of mortality alone and a composite outcome consisting of mortality and aortic valve replacement for AR in an asymptomatic population.

The results demonstrated that compared to mild AR, moderate AR is not a predictor for increased mortality but was a predictor for the composite outcome of mortality or aortic valve replacement for AR. Although the point estimate suggested increased events in the moderate AR group for mortality, imprecision was identified as the confidence interval crossed 1.0, meaning it was not a significant predictor for this outcome. This imprecision was not observed for the composite of mortality and aortic valve replacement for AR so moderate AR was a significant predictor for this composite outcome. Evidence was graded very low quality for the mortality outcome and low quality for the composite outcome of mortality and aortic valve replacement for AR.

Severe MR

One study reported data for the prognostic effect of severe MR, defined as effective regurgitant orifice area >40 mm^2, compared to mild MR (effective regurgitant orifice area <20 mm^2) in terms of all-cause mortality in an asymptomatic population. The results demonstrated that severe MR is associated with increased mortality compared to those with mild MR, with no imprecision identified and evidence being graded low quality.

One study reported data for the prognostic effect of severe MR compared to moderate MR in terms of mortality and mitral valve surgery in an asymptomatic population. The results demonstrated that severe MR is associated with increased mortality and increased mitral valve surgery compared to those with moderate MR. Although the confidence intervals

touched 1.0 for the mortality outcome, severe MR was a significant predictor of outcome in both cases as confidence intervals did not cross the null line. Evidence was graded very low and low quality for these outcomes.

Moderate MR

One study reported data for the prognostic effect of moderate MR, defined as effective regurgitant orifice area 20-39 mm^2, compared to mild MR (effective regurgitant orifice area <20 mm^2) in terms of all-cause mortality in an asymptomatic population. The results demonstrated that moderate MR is associated with increased mortality compared to those with mild MR, with no imprecision identified and evidence being graded low quality.

Severe functional TR

Two different studies investigated the prognostic effect of severe functional TR. One study compared this to trivial functional TR in a population with heart failure with reduced ejection fraction and the other compared it to trivial, mild or moderate functional TR in those with functional TR due to systolic left ventricular dysfunction. In one study there was a mixture of asymptomatic and symptomatic patients and the other study included only asymptomatic patients.

One study defined severe functional TR according to American Society of Echocardiography guidelines and the results from two separate models suggested that severe functional TR is associated with increased mortality compared to those with trivial functional TR, with no imprecision identified and evidence being graded moderate quality.

The second study defined severe functional TR as effective regurgitant orifice area ≥0.4 cm^2 and the results demonstrated that severe functional TR was associated with increase all-cause mortality compared to those with trivial, mild or moderate functional TR, with no imprecision identified and evidence being graded low quality.

Overall, the results from both studies suggest that severe functional TR may be associated with increased mortality compared to those with non-severe functional TR, though the two studies differed in the comparator used.

Moderate functional TR

One study reported data for the prognostic effect of moderate functional TR, graded according to American Society of Echocardiography guidelines, compared to trivial functional TR in a population with heart failure with reduced ejection fraction in terms of mortality.

The results from two separate models suggested that moderate functional TR is associated with increased mortality compared to those with trivial functional TR, with no imprecision identified, despite the lower confidence interval of one of both models coming close to 1.0, and evidence being graded low quality.

Prognostic factor indirectness was also present as the study combines symptomatic and asymptomatic moderate functional TR as a single prognostic factor rather than looking individually at symptomatic moderate and asymptomatic moderate functional TR as prognostic factors

Overall discussion of evidence and contribution to recommendations

Overall, the committee agreed that the evidence included in this review demonstrates increased events in those with moderate and/or severe valve disease, with most studies demonstrating these to be significant predictors of outcome, compared to mild or mild and

moderate valve disease, depending on the specific comparisons in each study. Although there were only one or two studies for moderate and severe valve disease for each specific type of valve disease and the majority of the evidence was low or very low quality, the evidence across studies consistently suggested increased events in those with moderate and severe valve disease relative to the specific comparator used in each study, with most reporting them to be significant predictors of outcome. The committee combined this with their knowledge of current practice in terms of specialist referral and agreed that those with moderate or severe valve disease would be referred to a specialist in current practice, regardless of the type of valve disease. Therefore, a recommendation to offer referral to a specialist was made for those with moderate or severe valve disease of any type, including primary and secondary valve disease, and it was agreed that this would not represent a change in practice.

In terms of mild valve disease, it was agreed that although increased events were observed in moderate and severe valve disease across the evidence, this could not be used as evidence to recommend that mild disease is never referred to a specialist, as the review did not allow for comparisons of outcome between those with mild valve disease and those with no valve disease. However, it was stressed that mild valve disease is very common within the population, particularly those over 70 years of age, and that mild valve disease is seldom the cause of symptoms and in the vast majority of cases mild valve disease does not progress. It was agreed that recommending that mild valve disease be referred to a specialist, even as a consider recommendation, was not appropriate as in general mild valve disease does not require specialist referral and a recommendation could lead to services becoming overwhelmed with referrals. It was however noted that there may be some cases where mild valve disease may be referred, particularly mild bicuspid aortic stenosis, and that in primary care it would be unusual for bicuspid aortic stenosis, even if only mild, not to be referred to a specialist as it is very different to other forms of mild valve disease in terms of progression. Based on the discussion, the committee agreed to make a recommendation covering mild valve disease, which was to advise people that mild valve disease is not often the cause of symptoms and rarely progresses but that they should seek advice from a health professional if they develop symptoms. In terms of current practice for mild valve disease, the committee noted that it varies and that there are cases of mild valve disease that are unnecessarily referred to a specialist. This is why a recommendation to advise people that mild heart valve disease is not usually the cause of symptoms but to seek advice from a health professional if symptoms develop, rather than referring those with mild heart valve disease to a specialist, was made. Although the recommendation on mild valve disease does not preclude referral of mild valve disease, it may help to reduce the number of cases referred unnecessarily by highlighting that in most cases symptoms are not caused by mild valve disease and it is unlikely to progress, and the recommendation should not lead to an increase in mild cases of valve disease being referred.

A recommendation to offer specialist assessment to people with bicuspid aortic valve disease of any severity was also made based on consensus and committee experience. This is because bicuspid aortic valve disease is a congenital disease that progresses much more rapidly than progressive/degenerative disease, can be associated with aortopathy and needs specialist care sooner. It was agreed that an offer recommendation was appropriate as in practice it is usually referred. The committee discussed whether adults with mitral valve prolapse and a documented ventricular arrythmia should also be referred based on the possible increased risk of sudden death. However, as any patient with ventricular tachycardia would require assessment by a cardiologist, irrespective of the presence of mitral valve prolapse, the indication would be the arrhythmia, and not the mitral valve prolapse so it was not appropriate to include this within this guideline.

Referral to a specialist for each of the recommended groups was important due to the increased negative events in these groups, demonstrated in the evidence for moderate and severe valve disease and based on committee experience for bicuspid aortic valve disease. Being referred to a specialist allows these groups to be monitored as appropriate and

treatment options considered in order to limit negative outcomes occurring. If they were not referred to a specialist, progression or complications of the disease may be identified later and result in a worse outcome. Referring to a specialist was also important in terms of informing the patient about their condition and what to expect over time in terms of progression and treatment options. The committee noted that services would be improved if the echocardiogram report generated an automatic cardiology referral where appropriate (i.e. moderate to severe valve disease).

1.1.12.4 Cost effectiveness and resource use

There was no published evidence of cost-effectiveness. The committee were presented with the unit cost of a first outpatient cardiology visit. A recommendation was made offering referral to a specialist for people with moderate or severe heart valve disease of any type.

The committee noted that a large part of the elderly population, around one third of the over 65s, has a mild form of heart valve disease which rarely causes symptoms nor progresses to more serious stages of the disease. The committee acknowledged that, in most cases, there is no need to refer patients with mild heart valve disease to specialist care if there are no other concerns. Hence, the committee decided to add a second recommendation highlighting the fact that very rarely mild heart valve disease is symptomatic and progresses over the years.

Overall, this recommendation should reduce the number of patients with mild heart valve disease referred to specialist care which should reduce the cost for the NHS, improve its efficiency, and shorten the waiting time for other patients in need of a specialist visit.

1.1.12.5 Other factors the committee took into account

Although no recommendation for referral to a specialist was made for those with mild valve disease, the committee did discuss the psychological effect that being referred to a specialist may have on patients with mild valve disease, which may differ for different patients. For example, for some being referred may help ease their concerns about progression of the disease while for others being referred to a specialist may make them feel that their condition is more serious and increase anxiety.

1.1.13 Recommendations supported by this evidence review

This evidence review supports recommendations 1.1.6-1.1.7.

Appendices

1.1.14 References

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Appendix A – Review protocols

Review protocol for indications for referral to a specialist following echocardiography

ID	Field	Content
0.	PROSPERO registration number	CRD42019158280
1.	Review title	In adults with heart valve disease who have had echocardiography, what are the indications for referral to a specialist?
2.	Review question	In adults with heart valve disease who have had echocardiography, what are the indications for referral to a specialist?
3.	Objective	To determine which echocardiography findings, with or without accompanying symptoms require referral to a specialist in adults with 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 relevant 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	Inclusion: Adults aged 18 years and over with diagnosed heart valve disease who have had echocardiography, 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 less than 18 years. Adults with congenital heart disease (excluding bicuspid aortic valves). Tricuspid stenosis and pulmonary valve disease. 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.	Indications for referral	• Severe valve disease (± symptoms) • Moderate valve disease + asymptomatic • Moderate valve disease + symptomatic *Severity assessed by echo and rated as per British Society of Echocardiography criteria* *Symptom status from clinical assessment*
8.	Confounding factors	Key confounding factors: • Left ventricular ejection fraction • Left ventricular stroke volume index • Coexistent second heart valve disease • Co-existing coronary disease • Age • Frailty (e.g., CSHA, Katz score)
9.	Types of study to be included	• Prospective and retrospective cohort studies that control for confounders in the study design or analysis • Systematic reviews of the above • If no cohort studies are identified case control studies that control for confounders in the study design or analysis will be included but downgraded for risk of bias.
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
11.	Context	N/A

12.	Primary outcomes (critical outcomes)	Need for referral based on: • Mortality (without intervention after follow-up ≥12 months) • NYHA class change by 2 classes (e.g. class II to class IV; or hospital admission for heart failure) (after follow-up ≥12 months) • Need for intervention 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). This will include study design, analysis method, population source, baseline population characteristics, confounding factors accounted for, numbers in each prognostic group, numbers of events, and calculated effect estimate when reported.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. • The QUIPs checklist will be used to assess risk of bias of each individual study.

		10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
16.	Strategy for data synthesis	• Pooling will be considered if the population, prognostic factor, outcomes, confounders and analysis are sufficiently similar. It is not necessary for the exact same confounders to be adjusted for because only the key confounders, with higher coefficients of determination, will noticeably affect the effect size. Many of the other confounders will have a relatively small effect on the point estimate so it may be appropriate to pool studies with slightly different arrays of confounding variables. This is judged on a case-by-case basis. • Where data allows, pairwise meta-analysis will be performed using Cochrane Review manager (RevMan5) software. A fixed-effect meta-analysis, with hazard ratios, odds ratios or risk ratios (as appropriate), and 95% confidence intervals will be calculated for each outcome. • Data from the meta-analysis will be presented and quality assessed in adapted GRADE tables taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each risk factor. Publication or other bias will only be taken into consideration in the quality assessment if there are 5 or more studies in the analysis. • Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic. We will consider an I^2 value greater than 50% indicative of substantial heterogeneity. We will conduct sensitivity analyses based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity

		in effect estimates. If this does not explain the heterogeneity, the results will be presented using random-effects. • If meta-analysis is not possible or appropriate, results will be reported individually per outcome in adapted GRADE tables. • A second reviewer will quality assure 10% of the data analyses. Discrepancies will be identified and resolved through discussion (with a third party where necessary).	
17.	Analysis of sub-groups	**Groups that will be analysed separately (strata):** • Type of heart valve disease: o aortic [including bicuspid] stenosis o aortic regurgitation o mitral stenosis o mitral regurgitation o tricuspid regurgitation **Subgroups that will be investigated if heterogeneity is present:** • Age (<75 / ≥75 years) • Single vs multiple valve disease • Co-existing coronary disease 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		
20.	Country	England		
21.	Anticipated or actual start date	09/05/2019		
22.	Anticipated completion date	17/06/2021		
23.	Stage of review at time of this submission	Review stage	Started	Completed
		Preliminary searches	☑	☑
		Piloting of the study selection process	☑	☑
		Formal screening of search results against eligibility criteria	☑	☑
		Data extraction	☑	☑
		Risk of bias (quality) assessment	☑	☑
		Data analysis	☑	☑
24.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail		

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

28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10122	
29.	Other registration details	None	
30.	Reference/URL for published protocol		
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	Aortic regurgitation; aortic stenosis; diagnosis; echocardiography; heart valve disease; mitral regurgitation; mitral stenosis; primary care; referral; 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

Appendix B – Literature search strategies

Heart valve disease – search strategy 2 - indications for specialist referral following echocardiography

This literature search strategy was used for the following review:

- In adults with heart valve disease who have had echocardiography, what are the indications for referral to a specialist?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[105]

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 search for a prognostic review used the following approach

- Population AND Prognostic/risk factor terms

Table 19: 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.	Dyspnea/
33.	(breathless* or dyspn?ea or wheez*).ti,ab.
34.	shortness of breath.ti,ab.
35.	syncope/ or dizziness/
36.	(faint* or dizziness or syncop*).ti,ab.
37.	Cardiac arrhythmia/
38.	palpitat*.ti,ab.
39.	Cardiac arrhythm*.ti,ab.
40.	Edema/
41.	(oedema or edema).ti,ab.
42.	Chest pain/
43.	((chest or thorax) adj (pain* or tightness)).ti,ab.
44.	Exercise tolerance/
45.	((physical* or exercise or fitness) adj5 (fit* or train* or therap* or activ* or strength or endur* or exert* or capacit* or tolera*)).ti,ab.
46.	or/32-45
47.	31 and 46
48.	Asymptomatic Diseases/
49.	asymptomatic.ti,ab.
50.	(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.
51.	or/48-50
52.	31 and 50
53.	47 or 52

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.	*dyspnea/
31.	(breathless* or dyspn?ea or wheez*).ti,ab.
32.	shortness of breath.ti,ab.
33.	*dizziness/ or *faintness/
34.	(faint* or dizziness or syncop*).ti,ab.
35.	*heart arrhythmia/
36.	palpitat*.ti,ab.
37.	Cardiac arrhythm*.ti,ab.
38.	*edema/
39.	(oedema or edema).ti,ab.
40.	*thorax pain/
41.	((chest or thorax) adj (pain* or tightness)).ti,ab.
42.	*exercise tolerance/
43.	((physical* or exercise or fitness) adj5 (fit* or train* or therap* or activ* or strength or endur* or exert* or capacit* or tolera*)).ti,ab.
44.	or/30-43
45.	29 and 44
46.	asymptomatic disease/
47.	asymptomatic.ti,ab.
48.	(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.
49.	or/46-48
50.	29 and 49
51.	45 or 50

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: [Dyspnea] this term only
#11.	(breathless* or dyspnea or dyspnoea or wheez*):ti,ab
#12.	MeSH descriptor: [Dizziness] this term only
#13.	MeSH descriptor: [Syncope] this term only
#14.	(faint* or dizziness or syncop*):ti,ab
#15.	shortness of breath:ti,ab
#16.	MeSH descriptor: [Arrhythmias, Cardiac] this term only
#17.	palpitat*:ti,ab
#18.	cardiac NEXT arrhythm*:ti,ab
#19.	MeSH descriptor: [Edema] this term only
#20.	(oedema or edema):ti,ab
#21.	MeSH descriptor: [Chest Pain] this term only
#22.	((chest or thorax) NEXT (pain* or tightness)):ti,ab
#23.	MeSH descriptor: [Exercise Tolerance] this term only
#24.	((physical* or exercise or fitness) near/5 (fit* or train* or therap* or activ* or strength or endur* or exert* or capacit* or tolera*)):ti,ab
#25.	(or #10-#24)
#26.	#9 and #25
#27.	MeSH descriptor: [Asymptomatic Diseases] this term only
#28.	asymptomatic:ti,ab
#29.	(symptom* near/3 (absent or non or none or no or missed or missing or unseen or subclinical)):ti,ab
#30.	"not apparent":ti,ab
#31.	"clinically silent":ti,ab
#32.	(or #27-#31)
#33.	#9 and #32
#34.	#26 or #33

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 20: 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

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

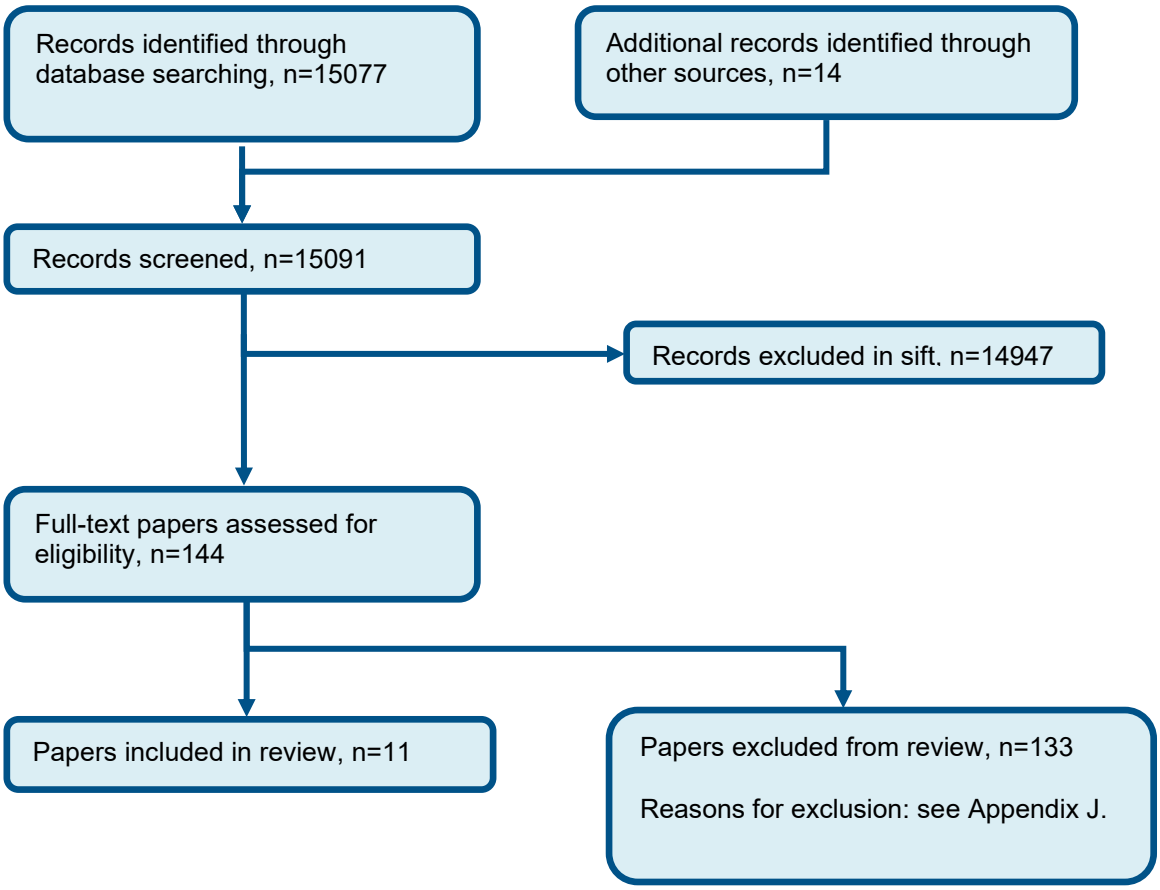
NHS EED and HTA (CRD) search terms

#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

Appendix C –Prognostic evidence study selection

Figure 1: Flow chart of clinical study selection for the review of indications for referral to a specialist following echocardiography



Note: Two search libraries were sifted for this review question – 'In adults with heart valve disease who have had echocardiography, what are the indications for referral to a specialist?' and 'What are the indications that interventions should be offered to adults with asymptomatic, severe heart valve disease?'

Appendix D –Prognostic evidence

D.1 Aortic stenosis

Reference	Bae 2020[10]
Study type and analysis	Retrospective cohort Cox proportional hazards analysis Republic of Korea
Number of participants and characteristics	N=148 NYHA class III-IV (symptomatic), n=34 NYHA class I-II (asymptomatic/minimally symptomatic), n=114 **Inclusion criteria:** 1) age > 18 years, 2) AS patients with moderate grade (any one of the three criteria was met: peak aortic jet velocity between 3.0 and 4.0 m/s on Doppler echocardiography, mean transvalvular pressure gradient between 30 and 40 mmHg, and aortic valve area by continuity equation between 1.0 (aortic valve area index more than 0.6 cm2/m2) and 1.5 cm2), and 3) no or any secondary or functional regurgitation or stenotic valvular disease (except AV) less than or equal to moderate-to-severe grade. **Exclusion criteria:** Mild or severe AS grade; with primary or intrinsic severe valvular disorder other than AV; who underwent surgical correction of any valvular disease; had suffered a dyspnoea with New York Heart Association (NYHA) functional class IV; had renal replacement therapy, such as dialysis or transplantation; or had malignancy or active systemic inflammation or infection **Values listed below are presented as mean (SD) or number (%)** **Patient characteristics:** • Male: 79 (53.4%) • Age: 69.3 (11.2) years

Reference	Bae 2020[10]
	• Hypertension, 68 (45.9%) • Diabetes mellitus, 43 (29.1%) • Coronary artery disease, 34 (23%) • Prior atrial fibrillation, 34 (23%) **Population source:** those matching inclusion criteria from echocardiography laboratories of one tertiary centres between 2008 and 2012. Follow-up data obtained retrospectively from medical record review. Of 279 patients who were screened, 131 were excluded because of the incompleteness of minimum follow-up requirements of five years in cases with absent CV clinical outcomes.
Prognostic variables	NYHA class III-IV (symptomatic) NYHA class I-II (asymptomatic/minimally symptomatic; referent)
Confounders	Significant variables in the univariate Cox analysis were entered into the multivariate model: Diabetes, AV area < 1.25 cm2, moderate or moderate-to-severe MR, LVEF, E/e', LVESD, IVRT, NT pro-BNP, creatinine, very high CV risk
Outcomes and effect sizes	**Composite of CV death, AV replacement, and hospitalization for worsening heart failure after the index echocardiography– medically managed initially** **HR 3.838 (1.721 to 8.561) for NYHA class III-IV vs. NYHA class I-II in moderate AS** 16 CV deaths, 32 AV replacements, and 31 HF cases occurred during follow-up. This was a total of 79 people with events, 34 of whom were NYHA III-IV Mean follow-up: 5.6 years. Follow-up data were evaluated for primary outcomes by reviewing medical records or through telephone interviews. The 5-year follow-up completeness was 100%
Comments, risk of bias and indirectness	Risk of bias: 1. Study participation HIGH 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement HIGH 5. Study confounding HIGH 6. Statistical analysis HIGH 7. Other risk of bias LOW

Reference	Bae 2020[10]
	OVERALL RISK OF BIAS VERY HIGH Indirectness: • Prognostic factor indirectness – prognostic groups are split into asymptomatic/minimally symptomatic and symptomatic groups based on NYHA classes of I-II and III-IV, respectively. Ideally would be interested in asymptomatic vs. any symptoms in line with the protocol. Outcome indirectness – composite of outcomes included in the protocol. • Confounding factors: although the multivariate analysis includes some of the confounders pre-specified in the protocol (LVEF, and co-existent second heart valve disease), others are not included (age, LV stroke volume index, frailty, and co-existent coronary disease).

Reference	Delesalle 2019[35]
Study type and analysis	Retrospective cohort Cox proportional hazards analysis France
Number of participants and characteristics	N=508 NYHA class III-IV (symptomatic), n=69 NYHA class I-II (asymptomatic/minimally symptomatic), n=439 **Inclusion criteria:** Moderate aortic stenosis (defined as aortic valve area on echocardiography between 1.0 and 1.5 cm^2); aged ≥18 years; left ventricular ejection fraction ≥50% **Exclusion criteria:** More than mild aortic or mitral regurgitation; prosthetic valves; congenital heart disease (with exception of bicuspid aortic valves); supravalvular or subvalvular aortic stenosis; dynamic left ventricular outflow tract obstruction; and individuals declining to participate in the study.

Reference	Delesalle 2019[35]

	Values listed below are presented as mean (SD) or number (%)
	
	Patient characteristics:
	• Male/female: 287/221 (56.5%/43.5%)
	• Age: 75 (11) years
	• Body surface area: 1.91 (0.22) m^2
	• Symptomatic status:
	  ○ Asymptomatic or minimally symptomatic (NYHA class I-II), 439 (86.4%)
	  ○ Symptomatic (NYHA class III-IV), 69 (13.6%)
	• Hypertension, 398 (78.3%)
	• Diabetes mellitus, 184 (36.2%)
	• Hyperlipidaemia, 246 (48.4%)
	• Smoking, 83 (16.3%)
	• Coronary artery disease, 236 (46.5%)
	• Myocardial infarction, 39 (7.7%)
	• Left bundle branch block, 28 (5.5%)
	• Prior atrial fibrillation, 171 (33.7%)
	• Heart failure, 45 (8.9%)
	• Charlson comorbidity index: 2.04 (2.03)
	
	• Aortic valve area: 1.2 (0.15) cm^2
	• Peak aortic jet velocity: 3.2 (0.55) m/s
	• Mean pressure gradient: 24.8 (9.0) mmHg
	• Indexed stroke volume: 44 (10.0) ml/m^2
	• Moderate-severe valve calcification, 276 (53%)
	• LV end-diastolic diameter: 48.6 (7.0) mm
	• LV end-systolic diameter: 30.0 (6.0) mm
	• LV ejection fraction: 64.0 (8.0)%
	• Indexed LV mass: 149.0 (64.0) g/m^2

Reference	Delesalle 2019[35]
	• Left atrial volume index: 37.0 (20.0) ml/m^2 • Aortic valve replacement during follow-up, 113 (22.3%) **Population source:** those matching inclusion criteria from echocardiography laboratories of two French tertiary centres (Amiens and Lille) between 2000 and 2014. Follow-up data obtained retrospectively from database.
Prognostic variables	NYHA class III-IV (symptomatic) NYHA class I-II (asymptomatic/minimally symptomatic; referent)
Confounders	For mortality, a pre-defined multivariate Cox proportional hazards model included the following covariates considered to have potential prognostic impact: age, sex, body surface area, New York Heart Association class, prior atrial fibrillation, mean transaortic pressure gradient, left ventricular ejection fraction, history of myocardial infarction, moderate-severe aortic valve calcification, Charlson comorbidity index and aortic valve replacement (treated as a time-dependent variable). Two models are reported in the study, one with and one without the addition of aortic valve replacement as a covariate. The model with this adjustment has been extracted as this is an important factor that may have affected the results.
Outcomes and effect sizes	**All-cause mortality – medically managed initially as there was an option to perform surgery when progressed to severe AS – analysis adjusted for aortic valve replacement being performed during follow-up** **HR 1.04 (0.89 to 1.21) for NYHA class III-IV vs. NYHA class I-II in moderate AS** A total of 255 deaths occurred during follow-up, with 101 of these being cardiovascular related. Mortality rates were 22±3% at 2 years, 36±2 at 4 years and 47±3 at 6 years of follow-up. Median (IQR) follow-up: 47 (24-80) months. Information on follow-up was obtained yearly on the same period for entire cohort by direct patient interview, clinical examination, and/or repeated follow-up letters, questionnaires and telephone calls to physicians, patients and (if required) next of kin. In total, 246 (97%) of surviving patients were followed up until the end of the study (2016), meaning 3% were lost to follow-up.
Comments, risk of bias and indirectness	Risk of bias: 1. Study participation LOW 2. Study attrition LOW 3. Prognostic factor measurement HIGH 4. Outcome Measurement LOW 5. Study confounding HIGH

Reference	Delesalle 2019[35]
	6. Statistical analysis LOW 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH Indirectness: • Prognostic factor indirectness – prognostic groups are split into asymptomatic/minimally symptomatic and symptomatic groups based on NYHA classes of I-II and III-IV, respectively. Ideally would be interested in asymptomatic vs. any symptoms in line with the protocol. • Confounding factors: though the multivariate analysis includes some of the confounders pre-specified in the protocol (age and LVEF), others are not included (LV stroke volume index, frailty, co-existent second heart valve disease and co-existent coronary disease). Though some of these may be covered by the Charlson comorbidity index that was included in the analysis, others would not be included under this risk score and therefore not been adjusted for (downgraded for this in risk of bias so not downgraded further for indirectness).

Reference	Kearney 2013[71]
Study type and analysis	Prospective cohort study between 1988 and 1994 Multivariate forward stepwise logistic regression analysis Australia
Number of participants and characteristics	N=132 (n=239 overall, but only n=132 included in the analysis for progression to severe AS as required at least two transthoracic echocardiograms >6 months apart to have been performed and those already severe at baseline not relevant for the analysis) Moderate aortic stenosis, n=34 Mild aortic stenosis, n=98 Analysis focuses on those with mild or moderate aortic stenosis in >60 years of age population as the outcome is progression to severe aortic stenosis. Symptomatic status not reported. **Inclusion criteria:** >60 years old at university veterans' hospital with aortic stenosis (mean aortic valve gradient >10 mmHg); and at least two transthoracic echocardiograms >6 months apart to be included in analysis for severity progression

Reference	Kearney 2013[71]

	Exclusion criteria:
	Co-existent severe additional valve disease.
	
	Values listed below are presented as mean (SD) or number (%) and are for n=147 patients included in progression analysis, including n=15 that were severe at baseline and not included in the analysis for the outcome that has been extracted
	
	Patient characteristics:
	• Age: 73 (6) years (range 60-92 years)
	• Male/female: 121/26 (82%/18%)
	• Valve pathology
	  ○ Tri-leaflet degenerative calcific aortic stenosis, 89%
	  ○ Bicuspid stenosis, 3%
	  ○ Rheumatic, 3%
	  ○ Uncertain, 5%
	
	• Baseline aortic stenosis severity
	  ○ Mild, 98 (67%)
	  ○ Moderate, 34 (23%)
	  ○ Severe, 15 (10%)
	• Myocardial infarction, 56 (38%)
	• Congestive heart failure, 53 (36%)
	• Cerebrovascular disease, 26 (18%)
	• Peripheral vascular disease, 24 (16%)
	• Severe renal impairment, 13 (9%)
	• Anaemia, 40 (27%)
	• Diabetes mellitus, 26 (18%)
	• Hypertension, 104 (71%)
	• Hypercholesterolaemia, 47 (32%)
	• Current smoker, 11 (7%)

Reference	Kearney 2013[71]
	• Mean aortic valve gradient: 21 (11) mmHg • Initial aortic valve area: 1.4 (0.4) cm^2 • Left ventricular dysfunction, 19 (12%) • Left ventricular hypertrophy, 69 (47%) • Degenerative calcific stenosis, 131 (89%) • ≥ moderate aortic valve calcification, 48 (33%) • Serum estimated glomerular filtration rate: 61 (21) ml/min **Population source:** consecutive patients with aortic stenosis from Department of Veteran's Affairs >60 years from single Australian tertiary university veterans' hospital between 1988 and 1994.
Prognostic variables	Moderate aortic stenosis Mild aortic stenosis (referent) Indirectness: indirect based on protocol as ideally aimed to look at moderate symptomatic and moderate asymptomatic as separate prognostic variables, but not provided in this study. Patients were retrospectively re-classified according to current AHA/ACC guidelines: mild (aortic valve area >1.5 cm^2 or mean aortic valve gradient <25 mmHg); moderate (aortic valve area 1.0-1.5 cm^2 or mean aortic valve gradient 25-40 mmHg) or severe (aortic valve area <1.0 cm^2 or mean aortic valve gradient >40 mmHg) aortic stenosis. Symptomatic status not reported.
Confounders	Two different multivariate forward stepwise logistic regression analysis models were performed, one which included aortic valve calcification and another that excluded it from the model as data for this variable was incomplete at 62% - unclear whether data were imputed for those with missing values or whether sample size reduced to exclude those without data for this variable. Clinically relevant variables with a P<0.05 on univariate analyses were incorporated into the models. Full list for each model is not explicitly stated as only those significant on multivariate analysis appear to be reported in the table, but the following had P<0.05 on univariate analysis and are therefore assumed to have been included in the multivariate models: duration of follow-up (per year), history of myocardial infarction, baseline aortic stenosis severity (moderate vs. mild), mean aortic valve gradient (per 10 mmHg) and aortic valve calcification (per grade; only in model 1). • Model 1: duration of follow-up (per year), history of myocardial infarction, baseline aortic stenosis severity (moderate vs. mild), mean aortic valve gradient (per 10 mmHg) and aortic valve calcification (per grade). • Model 2: duration of follow-up (per year), history of myocardial infarction, baseline aortic stenosis severity (moderate vs. mild) and mean aortic valve gradient (per 10 mmHg)

Reference	Kearney 2013[71]
Outcomes and effect sizes	**<u>Progression to severe aortic stenosis during follow-up – medically managed as follow-up was censored at time of aortic valve replacement or death</u>** **Model 1: OR 5.72 (1.47 to 22.30) for moderate AS vs. mild AS at baseline** – adjusted for duration of follow-up (per year), history of myocardial infarction, mean aortic valve gradient (per 10 mmHg) and aortic valve calcification (per grade – note only 62% had complete data for this variable). **Model 2: OR 10.50 (3.76 to 29.0) for moderate AS vs. mild AS at baseline** – adjusted for duration of follow-up (per year), history of myocardial infarction and mean aortic valve gradient (per 10 mmHg) *Note: indirect to outcomes listed in protocol but included as indirect evidence for need for intervention (though the study defines indication for intervention as severe symptomatic and there is no prognostic analysis for this end-point in the study).* During the study, progression to severe aortic stenosis occurred in 35% of those with mild aortic stenosis and 74% of those with moderate aortic stenosis at baseline. Patients were followed up prospectively until June 2008 by attendance for medical review and/or telephone review of the patient or managing physician. Follow-up was censored at aortic valve replacement or death. Mean follow-up 6.5 (4.3) years.
Comments, risk of bias and indirectness	Risk of bias: 1. Study participation — HIGH 2. Study attrition — LOW 3. Prognostic factor measurement — LOW 4. Outcome Measurement — LOW 5. Study confounding — VERY HIGH 6. Statistical analysis — HIGH 7. Other risk of bias — LOW OVERALL RISK OF BIAS — VERY HIGH *Note: the same risk of bias rating applies to both models reported for this prognostic factor* Indirectness: • Prognostic factor indirectness: moderate severity valve disease with/without symptoms used as prognostic factor, whereas ideally the aim was to look at moderate symptomatic and moderate asymptomatic valve disease as separate prognostic factors. This was not possible from this study and due to limited other available evidence was included in the review.

Reference	Kearney 2013[71]
	• Outcome indirectness: progression to severe valve disease is not listed as an outcome in the protocol but has been included as indirect evidence for need for intervention due to limited other available evidence. However, the study defines indication for intervention as severe + symptomatic and is therefore indirect as there is no information as to the symptomatic status of patients and therefore the requirement for intervention. • Confounders – though some multivariate analysis has been performed, none of the confounders pre-specified in the protocol were included in this analysis (downgraded for this in risk of bias so not downgraded further for indirectness).

Reference	Malouf 2012[92]
Study type and analysis	Retrospective cohort study Cox proportional hazards models USA
Number of participants and characteristics	N=360 **Severity based on valve area** <1.0 cm^2 (severe), n=96 ≥1.0 cm^2 (mild or moderate), n=264 **Severity based on mean gradient** ≥40 mmHg (severe), n=not reported <40 mmHg (mild or moderate), n=not reported Note that this study looked at various thresholds that are used to classify severity of aortic stenosis and did not classify patients into mild, moderate or severe by taking account of all the different values. Therefore, some may be considered severe based on the valve area but had a mean gradient consistent with mild or moderate aortic stenosis. **Inclusion criteria:** First diagnosis of native aortic stenosis between 1st January 1988 and 31st December 1997 (mild or greater, defined as valve area <2.0 cm^2 and mean gradient >10 mmHg).

Reference	Malouf 2012[92]

Exclusion criteria:
Age <18 years; life-threatening comorbid conditions at diagnosis; more than mild aortic regurgitation; and denied research authorisation.

Values listed below are presented as mean (SD) or number (%)

Patient characteristics:

Overall

- Age: 74 (14) years
- Male/female: 158/202 (44%/54%)
- Symptoms:
  - Any cardiac symptoms (typical or atypical chest pain or discomfort, dyspnoea, syncope or near syncope, or fatigue), 211 (59%)
  - Typical symptoms (syncope, near syncope, dyspnoea, or probable or typical angina), 165 (46%)
  - Severe symptoms (syncope, typical angina or class III-IV dyspnoea), 74 (21%)
  - Class III/IV (class III/IV dyspnoea or typical angina), 41 (11%)

- Atrial fibrillation, 65 (18%)
- Hypertension, 208 (58%)
- Coronary disease, 101 (28%)
- Comorbidity index: 4.4 (3.1)
- Systolic blood pressure: 146 (22) mmHg
- Creatinine (mean, IQR): 1.1 (0.9-1.3) mg/dL

- Valve area: 1.23 (0.36) cm^2
- Indexed valve area: 0.68 (0.22) cm^2/m^2
- Mean gradient: 22 (14) mmHg
- Peak velocity: 2.9 (0.82) m/s
- Aortic velocity ratio: 0.37 (0.11)

Reference	Malouf 2012[92]

	• Valve resistance: 121 (89) dynes/s/cm^{-5}
	• Stroke work loss: 13 (7)%
	• Ejection fraction: 60 (13)%
	
	Aortic valve area <1.0 cm^2
	• Age: 77 (15) years
	• Male/female: 43/53 (45%/55%)
	• Symptoms:
	  ○ Any cardiac symptoms (typical or atypical chest pain or discomfort, dyspnoea, syncope or near syncope, or fatigue), 62 (65%)
	  ○ Typical symptoms (syncope, near syncope, dyspnoea, or probable or typical angina), 54 (56%)
	  ○ Severe symptoms (syncope, typical angina or class III-IV dyspnoea), 21 (21%)
	  ○ Class III/IV (class III/IV dyspnoea or typical angina), 16 (17%)
	
	• Atrial fibrillation, 19 (20%)
	• Hypertension, 52 (54%)
	• Coronary disease, 25 (26%)
	• Comorbidity index: 4.4 (3.1)
	• Systolic blood pressure: 147 (23) mmHg
	• Creatinine (mean, IQR): 1.1 (0.9-1.4) mg/dL
	
	• Valve area: 0.79 (0.14) cm^2
	• Indexed valve area: 0.45 (0.10) cm^2/m^2
	• Mean gradient: 36 (19) mmHg
	• Peak velocity: 3.8 (0.93) m/s
	• Aortic velocity ratio: 0.25 (0.06)
	• Valve resistance: 225 (115) dynes/s/cm^{-5}
	• Stroke work loss: 19 (8)%
	• Ejection fraction: 56 (15)%
	
	Aortic valve area ≥1.0 cm^2

Reference	Malouf 2012[92]

	• Age: 72.31 (13.30) years
	• Male/female: 115/149 (44%/56%)
	• Symptoms:
	  ○ Any cardiac symptoms (typical or atypical chest pain or discomfort, dyspnoea, syncope or near syncope, or fatigue), 149 (56%)
	  ○ Typical symptoms (syncope, near syncope, dyspnoea, or probable or typical angina), 111 (42%)
	  ○ Severe symptoms (syncope, typical angina or class III-IV dyspnoea), 54 (21%)
	  ○ Class III/IV (class III/IV dyspnoea or typical angina), 25 (10%)
	
	• Atrial fibrillation, 46 (17%)
	• Hypertension, 156 (59%)
	• Coronary disease, 76 (29%)
	• Comorbidity index: 4.50 (3.07)
	• Systolic blood pressure: 146.30 (21.75) mmHg
	• Creatinine (mean, IQR):
	  ○ 1.1 (0.9-1.2) for 1.0-1.5 cm^2 aortic valve area group
	  ○ 1.1 (0.9-1.3) for ≥1.5 cm^2 aortic valve area group
	
	• Valve area: 1.39 (0.27) cm^2
	• Indexed valve area: 0.77 (0.19) cm^2/m^2
	• Mean gradient: 15.99 (6.32) mmHg
	• Peak velocity: 2.60 (0.47) m/s
	• Aortic velocity ratio: 0.41 (0.09)
	• Valve resistance: 83.54 (26.58) dynes/s/cm^{-5}
	• Stroke work loss: 10.33 (3.81)%
	• Ejection fraction: 60.66 (11.36)%
	
	Population source: all patients (in-patients or outpatients) with first diagnosis of native aortic stenosis (mild or greater) entered into database between 1st January 1988 and 31st December 1997 from Olmsted County community and referred to Mayo Clinic.

Prognostic variables	**Severity based on valve area** <1.0 cm^2 (severe)

Reference	Malouf 2012[92]
	≥1.0 cm^2 (mild or moderate) (referent) **Severity based on mean gradient** ≥40 mmHg (severe) <40 mmHg (mild or moderate) (referent) Aortic stenosis severity was assessed using Doppler echocardiography. Based on guidelines, mild, moderate and severe stenosis was defined as aortic valve area 1.5-2.0 cm^2, 1.0-1.5 cm^2 and <1.0 cm^2, respectively. Additionally, a peak velocity >4 m/s and mean gradient >40 mmHg are guideline-based thresholds for severe aortic stenosis.
Confounders	Variables included in the model differed depending on the outcome and prognostic factor. There is some uncertainty as to the full list included for each, but those that have clearly been included in the adjustment for each prognostic factor and outcome are listed below: • Severe AS based on valve area, for mortality outcome: valve area <1.0 cm^2, age, sex, comorbidity score, history of hypertension, atrial fibrillation, coronary disease and stroke/transient ischaemic attack. Possibly also included ejection fraction and class III-IV symptoms, but unclear. May have been others included but not well reported. • Severe AS based on valve area, for congestive heart failure outcome: valve area <1.0 cm^2, age, comorbidity score and atrial fibrillation. Possibly also included ejection fraction and class III-IV symptoms, but unclear. May have been others included but not well reported. • Severe AS based on valve area, for aortic valve replacement outcome: valve area <1.0 cm^2, age, sex, comorbidity score, atrial fibrillation, ejection fraction and class III-IV symptoms. May have been others included but not well reported. • Severe AS based on mean gradient, for aortic valve replacement outcome: mean gradient ≥40 mmHg, age, sex, comorbidity score, atrial fibrillation, ejection fraction and class III-IV symptoms. May have been others included but not well reported.
Outcomes and effect sizes	**Mortality after diagnosis – medically managed and censored at time of aortic valve replacement** **HR 1.81 (1.19 to 2.70) for aortic valve area <1.0 cm^2 (severe) vs. ≥1.0 cm^2 (mild or moderate)** *Note: study reports results as risk ratio rather than hazard ratio, but multivariate methods said to be by Cox proportional hazards which would generate a hazard ratio. Results have therefore been reported as hazard ratios.*

Reference	Malouf 2012[92]
	A total of 170 deaths were recorded during medical management and 10-year survival was 37±4%. Lower 5- and 8-year survival during medical management was observed in the <1.0 cm^2 group (40±6% and 18±6%, respectively) compared with the 1.0-1.5 cm^2 (73±3% and 54±4%, respectively) and ≥1.5 cm^2 groups (76±5% and 61±6%, respectively). **Congestive heart failure development – medically managed and censored at time of aortic valve replacement** **HR 2.30 (1.30 to 4.00) for aortic valve area <1.0 cm^2 (severe) vs. ≥1.0 cm^2 (mild or moderate)** A total of 80 patients developed congestive heart failure during conservative management, with a 10-year incidence of 39±4%. *Note: study reports results as risk ratio rather than hazard ratio, but multivariate methods said to be by Cox proportional hazards which would generate a hazard ratio. Results have therefore been reported as hazard ratios.* **Aortic valve replacement during follow-up – medically managed up until point aortic valve replacement performed** **HR 2.80 (1.60 to 4.60) for aortic valve area <1.0 cm^2 (severe) vs. ≥1.0 cm^2 (mild or moderate)** **HR 5.80 (3.00 to 11.10) for mean gradient ≥40 mmHg (severe) vs. <40 mmHg (mild or moderate)** Aortic valve replacement was performed in 131 patients, with 69 undergoing concomitant coronary bypass grafting. Aortic valve replacement was performed in 43 (45%) of those with a valve area <1.0 cm^2 and 88 (33%) of those with a valve area ≥1.0 cm^2. The 5-year incidence of aortic valve replacement was 55±7%, 17±3% and 9±3% for aortic valve area <1.0 cm^2, 1.0-1.5 cm^2 and ≥1.5 cm^2 groups. *Note: study reports results as risk ratio rather than hazard ratio, but multivariate methods said to be by Cox proportional hazards which would generate a hazard ratio. Results have therefore been reported as hazard ratios.* Mean follow-up: 7.5 (4.2) years. Follow-up was available for all but 1 patient (99.7% complete).
Comments, risk of bias and indirectness	Risk of bias: For mortality outcome – aortic valve area <1.0 cm^2 (severe) prognostic factor 1. Study participation LOW 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement LOW

Reference	Malouf 2012[92]	
	5. Study confounding	HIGH
	6. Statistical analysis	HIGH
	7. Other risk of bias	LOW
	OVERALL RISK OF BIAS	VERY HIGH
	<u>For congestive heart failure outcome – aortic valve area <1.0 cm^2 (severe) prognostic factor</u>	
	1. Study participation	LOW
	2. Study attrition	LOW
	3. Prognostic factor measurement	LOW
	4. Outcome Measurement	VERY HIGH
	5. Study confounding	HIGH
	6. Statistical analysis	HIGH
	7. Other risk of bias	LOW
	OVERALL RISK OF BIAS	VERY HIGH
	<u>For aortic valve replacement outcome – aortic valve area <1.0 cm^2 (severe) prognostic factor</u>	
	1. Study participation	LOW
	2. Study attrition	LOW
	3. Prognostic factor measurement	LOW
	4. Outcome Measurement	HIGH
	5. Study confounding	HIGH
	6. Statistical analysis	HIGH
	7. Other risk of bias	LOW
	OVERALL RISK OF BIAS	VERY HIGH
	<u>For aortic valve replacement outcome – mean gradient ≥40 mmHg (severe) prognostic factor</u>	
	1. Study participation	LOW
	2. Study attrition	LOW
	3. Prognostic factor measurement	LOW
	4. Outcome Measurement	HIGH
	5. Study confounding	HIGH

Reference	Malouf 2012[92]
	6. Statistical analysis VERY HIGH 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH Indirectness: <u>For mortality outcome – aortic valve area <1.0 cm^2 (severe) prognostic factor</u> • Confounders – though some multivariate analysis has been performed, only age and coronary disease pre-specified in the protocol were included in this analysis. Others listed in the protocol may be covered by the inclusion of the comorbidity index in multivariate analysis. Ejection fraction may also be included, but the reporting within the paper makes this unclear (downgraded for this in risk of bias so not downgraded further for indirectness). <u>For congestive heart failure outcome – aortic valve area <1.0 cm^2 (severe) prognostic factor</u> • Confounders – though some multivariate analysis has been performed, only age pre-specified in the protocol was included in this analysis. Others listed in the protocol may be covered by the inclusion of the comorbidity index in multivariate analysis. Ejection fraction may also be included, but the reporting within the paper makes this unclear (downgraded for this in risk of bias so not downgraded further for indirectness). <u>For aortic valve replacement outcome – aortic valve area <1.0 cm^2 (severe) prognostic factor</u> • Confounders – though some multivariate analysis has been performed, only age and ejection fraction pre-specified in the protocol were included in this analysis. Others listed in the protocol may be covered by the inclusion of the comorbidity index in multivariate analysis. In general, the reporting of factors included in the multivariate analyses was unclear (downgraded for this in risk of bias so not downgraded further for indirectness). <u>For aortic valve replacement outcome – mean gradient ≥40 mmHg (severe) prognostic factor</u> • Confounders – though some multivariate analysis has been performed, only age and ejection fraction pre-specified in the protocol were included in this analysis. Others listed in the protocol may be covered by the inclusion of the comorbidity index in multivariate analysis. In general, the reporting of factors included in the multivariate analyses was unclear (downgraded for this in risk of bias so not downgraded further for indirectness).

Reference	Rosenhek 2004[121]
Study type and analysis	Retrospective cohort study Cox proportional hazard models Austria
Number of participants and characteristics	N=176 Peak aortic jet velocity ≥ 3 m/s (moderate), n=120 Peak aortic jet velocity <3 m/s (mild), n=56 **Inclusion criteria:** Mild or moderate aortic stenosis (peak aortic jet velocity 2.5-3.9 m/s); asymptomatic; and normal left ventricular systolic function (left ventricular ejection fraction >50%). **Exclusion criteria:** Additional haemodynamically significant valve lesion (moderate-severe or severe). **Values listed below are presented as mean (SD) or number (%)** **Patient characteristics:** **Overall** • Age: 58 (19) years • Age ≥50 years, 134 (76%) • Male/female: 104/73 (59%/41%) • Aortic valve jet velocity: 3.13 (0.39) m/s • Aortic valve jet velocity ≥3 m/s, 120 (68%) • Aortic valve peak gradient: 40.0 (9.7) mmHg • Aortic valve mean gradient: 25.3 (7.4) mmHg • Moderate or severe aortic valve calcification, 81 (46%) • Coronary artery disease, 58 (33%)

Reference	Rosenhek 2004[121]
	• Hypertension, 72 (41%) • Diabetes mellitus, 37 (21%) • Hypercholesterolaemia, 60 (34%) **Population source:** consecutive patients matching inclusion criteria from single echocardiography laboratory between 1st January and 31st December 1994
Prognostic variables	Peak aortic jet velocity ≥ 3 m/s (moderate) Peak aortic jet velocity <3 m/s (mild) (referent) All patients underwent comprehensive examination including M-mode, 2D echocardiography, continuous wave, pulsed and colour Doppler by an experienced echocardiographer. Mild and moderate aortic stenosis were classified using peak aortic jet velocity <3 m/s and ≥ 3 m/s, respectively, among the included patients with peak aortic jet velocities between 2.9 and 3.9 m/s.
Confounders	The following variables appear to have been included in the multivariate model: age ≥50 years, gender, coronary artery disease, hypertension, diabetes, hypercholesterolaemia, aortic valve peak velocity ≥3 m/s (moderate) and aortic valve calcification score 3 or 4.
Outcomes and effect sizes	**Aortic valve replacement or death – medically managed initially as aortic valve replacement forms part of the outcome** **HR 1.60 (1.04 to 2.80) for peak aortic jet velocity ≥3 m/s (moderate) vs. <3 m/s (mild).** Note: paper reports results as a risk ratio, but methods suggest Cox proportional hazards are used which would produce a hazard ratio. Therefore, results have been reported as a hazard ratio. During follow-up, 67 events were observed, which included 33 aortic valve replacements and 34 deaths. Estimated survival free of events was 95±2%, 75±3% and 60±4% at 1, 3 and 5 years, respectively. Reason for surgery was severe symptomatic aortic stenosis (n=30) or need for coronary artery bypass grafting and aortic valve replaced at same time due to moderate aortic stenosis (n=3). Of the 34 deaths, 15 were cardiac-related. Severe aortic stenosis was recorded prior to death in 7 of these patients and aortic valve replacement was not performed for the following reasons: died on waiting list (n=2), patient refusal (n=2), advanced age and comorbidity (n=2) or unknown reasons (n=1). Reasons for 17 non-cardiac deaths were as follows: renal failure (n=3), respiratory failure (n=1), hepatic failure (n=3), cancer (n=4), perioperative mortality during non-cardiac surgery (n=4), suicide (n=1) and Parkinson's disease (n=1). In addition, there were 2 deaths where the cause was unknown. Median follow-up: 55 months (range, 1-76 months). Follow-up was complete for 171 (97%) patients.
Comments, risk of bias and indirectness	Risk of bias: 1. Study participation HIGH 2. Study attrition LOW 3. Prognostic factor measurement LOW

Reference	Rosenhek 2004[121]	
	4. Outcome Measurement	HIGH
	5. Study confounding	HIGH
	6. Statistical analysis	HIGH
	7. Other risk of bias	LOW
	OVERALL RISK OF BIAS	VERY HIGH
	Indirectness: • Confounders – though some multivariate analysis has been performed, only age and coronary artery disease pre-specified in the protocol were included in this analysis. The remaining pre-specified factors were not included (ejection fraction, stroke volume index, frailty and coexistent second heart valve disease) and also not reported in the patient characteristics table (downgraded for this in risk of bias so not downgraded further for indirectness).	

Reference	Tribouilloy 2015[137]
Study type and analysis	Retrospective cohort study Cox proportional hazards models France
Number of participants and characteristics	N=809 (898 enrolled but 89 subsequently excluded due to missing data or absence of follow-up) Study splits severe aortic stenosis (AS), which is based on aortic valve area (AVA) <1 cm^2 or indexed AVA <0.6 cm^2, into the following three groups: • **low-gradient low-flow severe AS** (LG/LF AS; AVA <1 cm^2, indexed AVA <0.6 cm^2, mean gradient <40 mmHg and stroke volume index <35 ml/m^2), n=57 • **low-gradient normal-flow severe AS** (LG/NF AS; AVA <1 cm^2, indexed AVA <0.6 cm^2, mean gradient <40 mmHg and stroke volume index ≥35 ml/m^2), n=85 • **high-gradient severe AS** (HG AS; AVA <1 cm^2, indexed AVA <0.6 cm^2 and mean gradient ≥40 mmHg), n=247 These three groups were compared with a group consisting of **mild-moderate AS** (AVA ≥1 cm^2 or indexed AVA ≥0.6 cm^2, and mean gradient <40 mmHg), n=420.

Reference	Tribouilloy 2015[137]

Inclusion criteria:
≥18 years old; diagnosed with ≥mild aortic stenosis (aortic valve calcification with reduction in systolic movements and aortic valve area <2 cm^2; ejection fraction ≥50%; and medically managed for at least 3 months following diagnosis.

Exclusion criteria:
>mild aortic and/or mitral regurgitation; prosthetic valves; congenital heart disease; supravalvular or subvalvular aortic stenosis; dynamic left ventricular outflow tract obstruction; ejection fraction <50%; patients that denied authorisation for research participation; missing data; and absence of follow-up.

Values listed below are presented as mean (SD) or number (%)

Patient characteristics:

LG/LF severe AS

- Age (median, IQR): 78.5 (73.5-86.3) years
- Male/female: 24/33 (42.1%/57.9%)
- Body surface area: 1.86 (0.21) m^2
- Systolic blood pressure (median, IQR): 140 (120-156) mmHg
- NYHA class III-IV symptoms, 9 (15.8%)
- NYHA class:
  - I, 25 (43.9%)
  - II, 23 (40.4%)
  - III, 8 (14.0%)
  - IV, 1 (1.8%)
- Hypertension, 40 (70.2%)
- Smoking, 14 (24.6%)
- Dyslipidaemia, 16 (28.1%)
- Diabetes mellitus, 20 (35.1%)
- Coronary artery disease, 22 (38.6%)
- History of atrial fibrillation, 22 (38.6%)

Reference	Tribouilloy 2015[137]

	• Charlson comorbidity index (median, IQR): 2 (1-4)
	
	LG/NF severe AS
	• Age (median, IQR): 79.3 (73.9-83.9) years
	• Male/female: 33/52 (38.8%/61.2%)
	• Body surface area: 1.78 (0.23) m^2
	• Systolic blood pressure (median, IQR): 140 (130-150) mmHg
	• NYHA class III-IV symptoms, 6 (7.1%)
	• NYHA class:
	  ○ I, 42 (49.4%)
	  ○ II, 37 (43.5%)
	  ○ III, 6 (7.1%)
	  ○ IV, 0 (0%)
	• Hypertension, 65 (76.5%)
	• Smoking, 19 (22.4%)
	• Dyslipidaemia, 36 (42.4%)
	• Diabetes mellitus, 21 (24.7%)
	• Coronary artery disease, 28 (32.9%)
	• History of atrial fibrillation, 27 (31.8%)
	• Charlson comorbidity index (median, IQR): 2 (1-3)
	
	HG severe AS
	• Age (median, IQR): 76.9 (67.9-83.1) years
	• Male/female: 122/125 (49.4%/50.6%)
	• Body surface area: 1.88 (0.24) m^2
	• Systolic blood pressure (median, IQR): 138 (120-150) mmHg
	• NYHA class III-IV symptoms, 54 (21.9%)
	• NYHA class:
	  ○ I, 97 (39.3%)
	  ○ II, 96 (38.9%)

Reference	Tribouilloy 2015[137]
	○ III, 39 (15.8%) ○ IV, 15 (6.1%) • Hypertension, 162 (65.6%) • Smoking, 66 (26.7%) • Dyslipidaemia, 105 (42.5%) • Diabetes mellitus, 64 (25.9%) • Coronary artery disease, 89 (36.0%) • History of atrial fibrillation, 71 (28.7%) • Charlson comorbidity index (median, IQR): 1 (1-2) **Mild-moderate AS** • Age (median, IQR): 76.9 (67.4-83.2) years • Male/female: 249/171 (59.3%/40.7%) • Body surface area: 1.94 (0.22) m^2 • Systolic blood pressure (median, IQR): 140 (125-150) mmHg • NYHA class III-IV symptoms, 59 (14.0%) • NYHA class: ○ I, 196 (46.7%) ○ II, 165 (39.3%) ○ III, 46 (11.0%) ○ IV, 13 (3.1%) • Hypertension, 316 (75.2%) • Smoking, 126 (30.0%) • Dyslipidaemia, 186 (44.3%) • Diabetes mellitus, 138 (32.9%) • Coronary artery disease, 126 (30.0%) • History of atrial fibrillation, 146 (34.8%) • Charlson comorbidity index (median, IQR): 2 (1-4) **Population source:** consecutive patients matching inclusion criteria at two French echocardiography laboratories between 2000 and 2012.

Reference	Tribouilloy 2015[137]
Prognostic variables	• **LG/LF severe AS** (AVA <1 cm^2, indexed AVA <0.6 cm^2, mean gradient <40 mmHg and stroke volume index <35 ml/m^2) • **LG/NF severe AS** (AVA <1 cm^2, indexed AVA <0.6 cm^2, mean gradient <40 mmHg and stroke volume index ≥35 ml/m^2) • **HG severe AS** (AVA <1 cm^2, indexed AVA <0.6 cm^2 and mean gradient ≥40 mmHg) • **Mild-moderate AS** (AVA ≥1 cm^2 or indexed AVA ≥0.6 cm^2, and mean gradient <40 mmHg) (referent) Comprehensive Doppler echocardiography performed.
Confounders	Variables included in the multivariate models were as follows: severity classification, age, sex, body surface area, Charlson comorbidity index, symptoms at baseline, coronary artery disease, history of atrial fibrillation and ejection fraction. Model building techniques were not used and covariates selected were considered of potential prognostic impact on an epidemiological basis. Multiple adjusted models are reported and the one that has adjusted for most variables has been extracted.
Outcomes and effect sizes	**All-cause mortality – medically managed and censored at time of cardiac surgery** **HR 0.88 (0.53 to 1.48) for LG/LF severe AS vs. mild-moderate AS** **HR 1.06 (0.66 to 1.71) for LG/NF severe AS vs. mild-moderate AS** **HR 1.47 (1.03 to 2.07) for HG severe AS vs. mild-moderate AS** Management was solely medical in 588 patients. 4-year mortality with medical treatment was 28±3%, 34±8%, 29±7% and 31±5% for mild-moderate AS, LG/LF AS, LG/NF AS and HG AS, respectively. Aortic valve replacement was eventually performed in 221 patients (27%), but these were censored from the analysis at the time of surgery for the medical management treatment analysis. Median follow-up with medical management: 22.8 months (range, 7-53 months). Median overall follow-up: 39.0 months (range, 11-69 months).
Comments, risk of bias and indirectness	Risk of bias: For LG/LF severe AS prognostic factor 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

Reference	Tribouilloy 2015[137]	
	7. Other risk of bias	LOW
	OVERALL RISK OF BIAS	VERY HIGH
	<u>For LG/NF severe AS prognostic factor</u>	
	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
	<u>For HG severe AS prognostic factor</u>	
	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
	Indirectness: <u>Note: applicable for all three prognostic factors</u> • Prognostic factor indirectness – severe AS is split into three different groups that are each compared with the same referent of mild-moderate AS, rather than looking at severe AS as a whole as a prognostic factor as specified in the protocol. • Confounders – though some multivariate analysis has been performed, only age, ejection fraction and coronary disease pre-specified in the protocol were included in this analysis. The remaining pre-specified factors were not included (stroke volume	

Reference	Tribouilloy 2015[137]
	index, frailty and coexistent second heart valve disease) (downgraded for this in risk of bias so not downgraded further for indirectness).

D.2 Aortic regurgitation

Reference	Detaint 2008[36]
Study type and analysis	Prospective cohort study Cox proportional hazard models USA
Number of participants and characteristics	N=251 QASE-severe grade, n=93 QASE-moderate grade, n=107 QASE-mild grade, n=51 *Note: QASE refers to quantitative echocardiographic measurements in line with the quantitative American Society of Echocardiography (QASE) thresholds for aortic regurgitation grading.* **Inclusion criteria:** Asymptomatic aortic regurgitation of at least mild severity (standard colour-flow imaging); pure (no aortic stenosis present) and isolated (no other valve disease present) aortic regurgitation; ejection fraction ≥50%; and evaluated with quantitative echocardiography for aortic regurgitation degree and left ventricular volumes. **Exclusion criteria:** Symptoms at diagnosis; aortic dissection or ongoing endocarditis; functional aortic regurgitation due to hypertension; associated aortic systolic gradient ≥20 mmHg; concomitant mitral valve disease, congenital (other than bicuspid valve) or pericardial disease; previous valve repair or replacement; and ejection fraction <50%

Reference	Detaint 2008[36]

	Values listed below are presented as mean (SD) or number (%)
	
	Patient characteristics:
	Overall
	• Valve pathology:
	  ○ Degenerative disease (valve thickening, annular enlargement and central defect), 140 (55.8%)
	  ○ Bicuspid valve, 60 (23.9%)
	  ○ Dystrophic disease (thin leaflet, annular enlargement, with or without valve prolapse), 19 (7.6%)
	  ○ Rheumatic disease, 6 (2.4%)
	  ○ Chronic endocarditis lesions, 6 (2.4%)
	  ○ Miscellaneous, 20 (8.0%)
	
	• Vasodilator therapy ≥6 months during medical follow-up:
	  ○ Angiotensin-converting enzyme inhibitors, 100 (39.8%)
	  ○ Calcium channel blockers, 51 (20.35%)
	  ○ Angiotensin-receptor blockers, 31 (12.4%)
	
	QASE-severe
	• Age: 58 (18) years
	• Male/female: 78/15 (84%/16%)
	• Atrial fibrillation, 4 (4%)
	• Hypertension history, 39 (42%)
	• Diabetes, 7 (8%)
	• Charlson comorbidity index: 1.8 (2.4) arbitrary units
	• Systolic blood pressure: 140 (24) mmHg
	• Diastolic blood pressure: 64 (13) mmHg
	• LV ejection fraction: 67 (9)%
	• LV end-systolic diameter index: 20 (4) mm/m^2
	• LV end-diastolic volume index: 133 (35) ml/m^2
	• LV end-systolic volume index: 45 (22) ml/m^2
	• Left ventricular mass: 300 (89) g

Reference	Detaint 2008[36]
	• Jet to outflow tract width ratio: 49 (15)% • Regurgitant volume: 92 (32) ml/beat • Effective regurgitant orifice area: 41 (18) mm^2 **QASE-moderate** • Age: 62 (18) years • Male/female: 67/40 (63%/37%) • Atrial fibrillation, 6 (6%) • Hypertension history, 54 (51%) • Diabetes, 5 (5%) • Charlson comorbidity index: 2.2 (2.5) arbitrary units • Systolic blood pressure: 138 (20) mmHg • Diastolic blood pressure: 74 (10) mmHg • LV ejection fraction: 68 (9)% • LV end-systolic diameter index: 18 (3) mm/m^2 • LV end-diastolic volume index: 95 (18) ml/m^2 • LV end-systolic volume index: 31 (12) ml/m^2 • Left ventricular mass: 231 (72) g • Jet to outflow tract width ratio: 35 (13)% • Regurgitant volume: 41 (12) ml/beat • Effective regurgitant orifice area: 18 (6) mm^2 **QASE-mild** • Age: 62 (15) years • Male/female: 22/29 (43%/57%) • Atrial fibrillation, 1 (2%) • Hypertension history, 30 (58%) • Diabetes, 1 (2%) • Charlson comorbidity index: 1.3 (1.8) arbitrary units • Systolic blood pressure: 140 (24) mmHg

Reference	Detaint 2008[36]
	• Diastolic blood pressure: 77 (14) mmHg • LV ejection fraction: 71 (9)% • LV end-systolic diameter index: 17 (3) mm/m^2 • LV end-diastolic volume index: 73 (15) ml/m^2 • LV end-systolic volume index: 22 (9) ml/m^2 • Left ventricular mass: 187 (57) g • Jet to outflow tract width ratio: 27 (12)% • Regurgitant volume: 17 (5) ml/beat • Effective regurgitant orifice area: 7 (2) mm^2 **Population source:** consecutive patients matching inclusion criteria between 1991 and 2003 prospectively enrolled. Likely to be single centre but this is unclear.
Prognostic variables	QASE-severe grade QASE-moderate grade QASE-mild grade (referent) Aortic regurgitation severity was assessed using three validated methods, which were eventually averaged to calculate regurgitant volume and effective regurgitant orifice area (85% of patients had at least 2 of the 3 methods performed): Doppler based on aortic and mitral stroke volume measurement; quantitative 2D echocardiography based on left ventricular and mitral stroke volume; and proximal isovelocity surface area method analysing proximal flow convergence. QASE guidelines were used to define mild, moderate and severe aortic regurgitation as follows: mild, regurgitant volume <30 ml/beat and effective regurgitant orifice area <10 mm^2; moderate, regurgitant volume ≥30 ml/beat or effective regurgitant orifice area ≥10 mm^2 (but not reaching the severe criteria); severe, regurgitant volume ≥ 60 ml/beat or effective regurgitant orifice area ≥30 mm^2.
Confounders	Factors included in multivariate models included the following for each outcome: • Mortality: age, gender, AR quantitative classification, comorbidity score and ejection fraction. • Mortality or aortic valve replacement for aortic regurgitation: age, gender, AR quantitative classification, end-systolic volume index and comorbidity index.
Outcomes and effect sizes	**<u>Mortality – under conservative management</u>** **HR 4.1 (1.4 to 14.1) for QASE-severe AR vs. QASE-mild AR**

Reference	Detaint 2008[36]
	HR 2.1 (0.8 to 6.7) for QASE-moderate AR vs. QASE-mild AR A total of 33 deaths occurred under conservative management. Survival was 93±2% at 5 years and 78±4% at 10 years. Survival under conservative management at 5 years was 82±6%, 95±2% and 98±2% in QASE-severe, QASE-moderate and QASE-mild aortic regurgitation, respectively. **Mortality or aortic valve replacement for aortic regurgitation – under conservative management** **HR 12.9 (5.4 to 38.5) for QASE-severe AR vs. QASE-mild AR** **HR 4.0 (1.7 to 11.8) for QASE-moderate AR vs. QASE-mild AR** Cardiac surgery was performed for aortic regurgitation in 80 patients. Indications for aortic regurgitation surgery were occurrence of symptoms in n=38, LV dysfunction or enlargement in n=17, aortic aneurysm in n=11, infective endocarditis in n=3 and physician and/or patient preference in n=11. 10 year rate of surgery for aortic regurgitation was 36±4%. For survival free of surgery for aortic regurgitation, 113 events occurred, including 33 deaths and 80 surgeries, with a rate of 50±4% at 10 years. Survival free of surgery for aortic regurgitation at 10 years was 20±5%, 57±6% and 92±4% in QASE-severe, QASE-moderate and QASE-mild aortic regurgitation, respectively. Mean follow-up: 8 (3.8) years. Follow-up was >5 years in 188 patients and >10 years in 82 patients, and was complete up to death or 2006 in 97%.
Comments, risk of bias and indirectness	Risk of bias: For mortality outcome – QASE-severe as prognostic factor 1. Study participation HIGH 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement LOW 5. Study confounding HIGH 6. Statistical analysis HIGH 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH For mortality outcome – QASE-moderate as prognostic factor 1. Study participation HIGH

Reference	Detaint 2008[36]
	2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement HIGH 5. Study confounding HIGH 6. Statistical analysis LOW 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH <u>For mortality or AVR for AR outcome – QASE-severe as prognostic factor</u> 1. Study participation HIGH 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement LOW 5. Study confounding HIGH 6. Statistical analysis HIGH 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH <u>For mortality or AVR for AR outcome – QASE-moderate as prognostic factor</u> 1. Study participation HIGH 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement HIGH 5. Study confounding HIGH 6. Statistical analysis LOW 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH Indirectness: <u>For all prognostic factor and outcome combinations:</u> • Confounding factors – though the multivariate analysis includes some of the confounders pre-specified in the protocol (age and LVEF for mortality and age for mortality or AVR) and other valve disease was an exclusion criterion, others are not included

Reference	Detaint 2008[36]
	(LV stroke volume index, frailty and co-existent coronary disease). Though some of these may be covered by the Charlson comorbidity index that was included in the analysis, others would not be included under this risk score and therefore not been adjusted for (downgraded for this in risk of bias so not downgraded further for indirectness).

D.3 Mitral regurgitation

Reference	Enriquez-Sarano 2005[40]
Study type and analysis	Prospective cohort study Cox proportional hazard models USA
Number of participants and characteristics	N=456 ERO ≥40 mm^2 – equivalent to severe MR, n=198 ERO 20-39 mm^2 – equivalent to moderate MR, n=129 ERO <20 mm^2 – equivalent to mild MR, n=129 **Inclusion criteria:** At least mild holosystolic mitral regurgitation on colour-flow imaging due to organic mitral valve disease identified by 2D echocardiography; isolated and pure mitral regurgitation (without aortic valve disease or mitral stenosis); quantitatively assessed by authors using at least two Doppler echocardiographic methods; and asymptomatic at diagnosis. **Exclusion criteria:** Mitral regurgitation due to ischaemic heart disease or cardiomyopathy; minimal or early or late systolic regurgitation; structurally normal valves; associated mitral stenosis that was more than trivial; associated organic aortic or tricuspid disease; history of valve repair or replacement; congenital or pericardial heart disease; or an ejection fraction <50%. **Values listed below are presented as mean (SD) or number (%)**

Reference	Enriquez-Sarano 2005[40]
	Patient characteristics: **ERO ≥40 mm² – equivalent to severe MR** • Age: 61 (14) years • Male/female: 162/36 (82%/18%) • Charlson comorbidity index: 1.4 (2.0) • Atrial fibrillation, 20 (10%) • Mitral valve prolapse, 194 (98%) • History of hypertension, 67 (34%) • Diabetes, 8 (4%) • Systolic blood pressure: 133 (17) mmHg • Diastolic blood pressure: 76 (9) mmHg • Left ventricular diastolic diameter: 61 (6) mm • Left ventricular systolic diameter: 37 (6) mm • End-diastolic volume index: 129 (23) ml/m² • End-systolic volume index: 38 (140) ml/m² • Ejection fraction: 70 (8)% • Left ventricular mass: 251 (54) g • Left atrial volume: 133 (49) ml • Cardiac index: 2.6 (0.5) l/min/m² • Systolic pulmonary pressure: 42 (13) mmHg • Mitral jet area: 13 (6) cm² • Ratio of mitral jet area to left atrial area: 39 (17)% • Effective regurgitant orifice area: 64 (21) mm² • Regurgitant volume: 101 (29) ml/beat **ERO 20-39 mm² – equivalent to moderate MR** • Age: 65 (14) years • Male/female: 83/46 (64%/36%) • Charlson comorbidity index: 1.8 (2.2) • Atrial fibrillation, 8 (6%)

Reference	Enriquez-Sarano 2005[40]
	• Mitral valve prolapse, 108 (84%) • History of hypertension, 52 (40%) • Diabetes, 5 (4%) • Systolic blood pressure: 137 (18) mmHg • Diastolic blood pressure: 77 (12) mmHg • Left ventricular diastolic diameter: 54 (6) mm • Left ventricular systolic diameter: 34 (7) mm • End-diastolic volume index: 103 (16) ml/m^2 • End-systolic volume index: 31 (120) ml/m^2 • Ejection fraction: 70 (8)% • Left ventricular mass: 222 (55) g • Left atrial volume: 98 (44) ml • Cardiac index: 2.8 (0.5) l/min/m^2 • Systolic pulmonary pressure: 35 (9) mmHg • Mitral jet area: 8.6 (3.4) cm^2 • Ratio of mitral jet area to left atrial area: 32 (11)% • Effective regurgitant orifice area: 31 (5) mm^2 • Regurgitant volume: 57 (13) ml/beat **ERO <20 mm^2 – equivalent to mild MR** • Age: 64 (14) years • Male/female: 40/89 (31%/69%) • Charlson comorbidity index: 1.5 (2.2) • Atrial fibrillation, 13 (10%) • Mitral valve prolapse, 62 (48%) • History of hypertension, 61 (47%) • Diabetes, 8 (6%) • Systolic blood pressure: 137 (22) mmHg • Diastolic blood pressure: 77 (9) mmHg • Left ventricular diastolic diameter: 49 (4) mm

Reference	Enriquez-Sarano 2005[40]
	• Left ventricular systolic diameter: 31 (4) mm • End-diastolic volume index: 80 (17) ml/m^2 • End-systolic volume index: 26 (100) ml/m^2 • Ejection fraction: 68 (9)% • Left ventricular mass: 169 (54) g • Left atrial volume: 67 (27) ml • Cardiac index: 2.9 (0.5) l/min/m^2 • Systolic pulmonary pressure: 35 (7) mmHg • Mitral jet area: 5 (3) cm^2 • Ratio of mitral jet area to left atrial area: 23 (10)% • Effective regurgitant orifice area: 11 (5) mm^2 • Regurgitant volume: 21 (10) ml/beat **Population source:** patients matching inclusion criteria between 1991 and 2000 at single centre (Mayo Clinic).
Prognostic variables	ERO ≥40 mm^2 – equivalent to severe MR ERO 20-39 mm^2 – equivalent to moderate MR ERO <20 mm^2 – equivalent to mild MR (referent) Mitral regurgitation was quantified by at least two of three validated methods, with the results averaged to calculate the regurgitant volume per beat and the area of effective regurgitant orifice. In line with published guidelines, mild, moderate and severe mitral regurgitation are defined as a regurgitant volume of <30, 30-59 and ≥60 ml/beat, respectively, or an effective regurgitant orifice area of <20, 20-39 and ≥40 mm^2, respectively. Note that the study only provides prognostic results for severity based on the effective regurgitant orifice area, and not regurgitant volume, for outcomes relevant to the protocol.
Confounders	Note that multiple models with different numbers of confounding factors adjusted for were reported and the one with the most confounders adjusted for has been extracted for each prognostic factor. This model included the following factors: ERO threshold grouping, age, sex, ejection fraction, presence of diabetes and presence of atrial fibrillation.
Outcomes and effect sizes	**All-cause mortality – medically managed and censored at time of surgery** **HR 2.90 (1.33 to 6.32) for ERO ≥40 mm^2 (severe MR) vs. ERO <20 mm^2 (mild MR)** **HR 2.58 (1.25 to 5.40) for ERO 20-39 mm^2 (moderate MR) vs. ERO <20 mm^2 (mild MR)**

Reference	Enriquez-Sarano 2005[40]
	Note: reported to be risk ratios in the table and text but methods section suggests they should be hazard ratios as Cox proportional hazards reported to be used. Results have therefore been reported as hazard ratios. A total of 56 deaths were recorded during medical management. Survival rates were reported to be 96±1% at 1 year and 78±4% at 5 years. Mean follow-up post-diagnosis was 2.7 (2.9) years under medical management and 5.1 (2.9) years under medical and surgical management. Clinical management following diagnosis was medical only in 224 patients (49%) and was medical followed by surgery in 232 patients (51%). For the outcome, patients were censored from the analysis when surgery was performed.
Comments, risk of bias and indirectness	Risk of bias: <u>For ERO ≥40 mm^2 (severe MR) prognostic factor</u> 1. Study participation HIGH 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement LOW 5. Study confounding HIGH 6. Statistical analysis HIGH 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH <u>For ERO 20-39 mm^2 (moderate MR) prognostic factor</u> 1. Study participation HIGH 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement LOW 5. Study confounding HIGH 6. Statistical analysis HIGH 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH Indirectness:

Reference	Enriquez-Sarano 2005[40]
	For both ERO ≥40 mm^2 (severe MR) and ERO 20-39 mm^2 (moderate MR) prognostic factors: • Confounding factors – though the multivariate analysis includes some of the confounders pre-specified in the protocol (age and LVEF) and other valve disease was an exclusion criterion, others are not included (LV stroke volume index, frailty and co-existent coronary disease) (downgraded for this in risk of bias so not downgraded further for indirectness).

Reference	Penicka 2018[113]
Study type and analysis	Prospective cohort study Cox proportional hazards regression model
Number of participants and characteristics	**Total n=258** Numbers in different regurgitant volume categories not available **Inclusion criteria** 1) absence of symptoms, validated using a bicycle exercise test; (2) preserved left ventricular (LV) ejection fraction (>60%) using the biplane Simpson method; and (3) sinus rhythm. **Exclusion criteria** Mild or no OMR, presence of symptoms, reduced LV ejection fraction (≤60%), non-sinus rhythm, history of coronary artery disease, concomitant aortic regurgitation, intracardiac shunt, contraindication for MRI, and poor echocardiography image quality **Values listed below are presented as mean (SD), median (IQR) or number (%)** **Patient characteristics:** **Age:** 63 (14) years Male (%): 60 **Regurgitant volume on** MRI (ml): 55.7 **Population source**: Consecutive patients from 2 centres in Belgium and Czech Republic. Recruitment period January 2011 to December 2014

Reference	**Penicka 2018[113]**
	Follow up median 5.0 years (IQR 3.5–6.0 years) Analysis was performed by an operator blinded to the results of echocardiographic assessment and the symptomatic status of the patient.
Prognostic variable	Echo-derived organic mitral regurgitation category: severe (regurgitant volume ≥60 ml) vs moderate (regurgitant volume 30-59 ml)
Confounders	Age, sex and echo-derived LVESD
Outcomes and effect sizes	Indication for surgery The recommended indications for mitral valve surgery at the time of the study included development of symptoms, LV dysfunction (LV end-systolic diameter ≥45 mm or LV ejection fraction ≤60%), and new onset of atrial fibrillation or pulmonary hypertension (systolic pulmonary artery pressure >50 mm Hg at rest). However, the final decision whether to refer a patient for surgery was taken by the referring cardiologist together with the patient and GP. 38 (15%) patients died, 58 (22%) underwent mitral valve surgery, and 106 (41%) either died or developed indication for mitral valve surgery. **Adjusted hazard ratio for all-cause mortality** 1.21 (1.00–1.59) for severe vs moderate on echo **Adjusted hazard ratio for indication for mitral valve surgery** 1.50 (1.32–1.70) for severe vs moderate on echo
Comments	Risk of bias (both outcomes): 1. Study participation — LOW 2. Study attrition — LOW 3. Prognostic factor measurement — LOW 4. Outcome Measurement — HIGH 5. Study confounding — HIGH 6. Statistical analysis — LOW 7. Other risk of bias — LOW OVERALL RISK OF BIAS — VERY HIGH

Reference	Penicka 2018[113]
	Indirectness: • Prognostic factor indirectness: only reported as a continuous variable

D.4 Tricuspid regurgitation

Reference	Benfari 2019[16]
Study type and analysis	Retrospective cohort study between 2003 and 2011 Cox proportional hazards regression USA
Number of participants and characteristics	N=11,507 Severe functional tricuspid regurgitation, n=745 Moderate functional tricuspid regurgitation, n=2,255 Trivial functional tricuspid regurgitation, n=4,329 (reference group) *Note: additional group with mild functional tricuspid regurgitation was included but did not form part of the reference group (n=4178).* Those with heart failure with reduced ejection fraction and some degree of functional tricuspid regurgitation (trivial, mild, moderate or severe). **Inclusion criteria:** Aged ≥18 years; heart failure with reduced ejection fraction diagnosed between 2003 and 2011 (heart failure stage B or C based on guideline-based criteria with ejection fraction by echocardiography <50%); comprehensive clinical and echocardiographic characterisation at the Mayo Clinic within three months of their first encounter (within the same episode of care, usually within the same week); defined functional tricuspid regurgitation grading had been performed; and estimation of systolic pulmonary artery pressure at baseline by echocardiography. **Exclusion criteria:**

Reference	Benfari 2019[16]

	Previous valve surgery; presence of pacemaker/defibrillator leads through the tricuspid valve; organic tricuspid, aortic or mitral valve disease of moderate or severe degree (functional mitral regurgitation not excluded); and pericardial, congenital (patent foramen ovale not excluded), hypertrophic or infiltrative (amyloidosis, haemo-chromatosis or sarcoidosis) heart disease.
	
	Values listed below are presented as mean (SD) or number (%)
	
	Patient characteristics:
	<u>Trivial TR</u>
	• Age: 65 (15) years
	• Age >65 years: 2,249 (52%)
	• Male/female: 3069/1260 (65%/35%)
	• Heart rate: 75 (18) bpm
	
	• Diastolic blood pressure: 70 (13) mmHg
	• Symptoms:
	  ○ Heart failure stage C: 2,725 (63%)
	  ○ Dyspnoea: 1,978 (46%)
	  ○ Oedema: 937 (22%)
	  ○ Jugular venous distension: 184 (4%)
	
	• Systemic hypertension: 2,450 (57%)
	• Diabetes mellitus: 1,026 (24%)
	• Dyslipidaemia: 2,211 (51%)
	• Smokers: 1,409 (33%)
	• Atrial fibrillation: 454 (10%)
	• History of coronary artery disease: 2,665 (62%)
	• Chronic obstructive pulmonary disease: 610 (14%)
	• History of cancer: 1,030 (24%)
	• Charlson index: 2.84 (2.59)
	• Glomerular filtration rate <60: 1,123 (26%)
	• MAGGIC score: 16.6 (7.0)

Reference	Benfari 2019[16]

	• End-diastolic diameter index: 28.0 (4.0) mm/m^2
	• End-systolic diameter index: 22.0 (5.0) mm/m^2
	• Mass index: 121 (35) g/m^2
	• Ejection fraction: 38 (9)%
	• Cardiac index <1.8 L/min/m^2: 129 (3%)
	• Stroke volume: 80 (21) ml
	• Stroke volume index <35 ml/m^2: 1,255 (29%)
	• E: 0.74 (0.25) m/s
	• A: 0.78 (0.31) m/s
	• E/A: 1.07 (0.64)
	• Deceleration time: 206 (61) ms
	• E/e': 14.32 (7.53)
	• Mitral regurgitation >2+: 630 (15%)
	• Systolic pulmonary pressure: 33 (10) mmHg
	• Pulmonary hypertension: 264 (6%)
	• Right ventricular dysfunction >2+: 279 (6%)
	
	<u>Moderate TR</u>
	• Age: 71 (14) years
	• Age >65 years: 1,666 (74%)
	• Male/female: 1,296/959 (57%/43%)
	• Heart rate: 81 (20) bpm
	• Systolic blood pressure: 122 (22) mmHg
	• Diastolic blood pressure: 70 (14) mmHg
	• Symptoms:
	  ○ Heart failure stage C: 1,726 (77%)
	  ○ Dyspnoea: 1,335 (59%)
	  ○ Oedema: 931 (41%)
	  ○ Jugular venous distension: 248 (11%)

Reference	Benfari 2019[16]
	• Systemic hypertension: 1,409 (62%) • Diabetes mellitus: 590 (27%) • Dyslipidaemia: 1,032 (46%) • Smokers: 698 (33%) • Atrial fibrillation: 704 (31%) • History of coronary artery disease: 1,389 (62%) • Chronic obstructive pulmonary disease: 371 (16%) • History of cancer: 576 (26%) • Charlson index: 3.42 (2.75) • Glomerular filtration rate <60: 1,046 (46%) • MAGGIC score: 21.6 (6.9) • End-diastolic diameter index: 29.0 (5.0) mm/m^2 • End-systolic diameter index: 24.0 (5.0) mm/m^2 • Mass index: 124 (35) g/m^2 • Ejection fraction: 34 (9)% • Cardiac index <1.8 L/min/m^2: 227 (10%) • Stroke volume: 67 (21) ml • Stroke volume index <35 ml/m^2: 1,106 (49%) • E: 0.91 (0.28) m/s • A: 0.69 (0.39) m/s • E/A: 1.65 (1.04) • Deceleration time: 169 (53) ms • E/e': 19.82 (10.11) • Mitral regurgitation >2+: 1,137 (50%) • Systolic pulmonary pressure: 51 (14) mmHg • Pulmonary hypertension: 1,080 (48%) • Right ventricular dysfunction >2+: 676 (30%)

Reference	Benfari 2019[16]

	Severe TR
	• Age: 72 (13) years
	• Age >65 years: 554 (74%)
	• Male/female: 404/341 (54%/46%)
	• Heart rate: 81 (20) bpm
	• Systolic blood pressure: 118 (21) mmHg
	• Diastolic blood pressure: 69 (13) mmHg
	• Symptoms:
	  ○ Heart failure stage C: 637 (86%)
	  ○ Dyspnoea: 506 (68%)
	  ○ Oedema: 423 (57%)
	  ○ Jugular venous distension: 128 (17%)
	
	• Systemic hypertension: 418 (59%)
	• Diabetes mellitus: 178 (24%)
	• Dyslipidaemia: 287 (39%)
	• Smokers: 231 (31%)
	• Atrial fibrillation: 359 (48%)
	• History of coronary artery disease: 432 (58%)
	• Chronic obstructive pulmonary disease: 126 (17%)
	• History of cancer: 178 (24%)
	• Charlson index: 3.44 (2.53)
	• Glomerular filtration rate <60: 415 (56%)
	• MAGGIC score: 24.3 (6.9)
	
	• End-diastolic diameter index: 29.0 (5.0) mm/m^2
	• End-systolic diameter index: 24.0 (5.0) mm/m^2
	• Mass index: 121 (38) g/m^2
	• Ejection fraction: 32 (10)%
	• Cardiac index <1.8 L/min/m^2: 127 (17%)

Reference	Benfari 2019[16]
	• Stroke volume: 59 (19) ml • Stroke volume index <35 ml/m^2: 476 (64%) • E: 0.96 (0.29) m/s • A: 0.58 (0.27) m/s • E/A: 2.01 (1.27) • Deceleration time: 156 (42) ms • E/e': 20.39 (10.38) • Mitral regurgitation >2+: 475 (64%) • Systolic pulmonary pressure: 56 (16) mmHg • Pulmonary hypertension: 408 (54%) • Right ventricular dysfunction >2+: 379 (51%) **Population source:** patients from single clinic (Mayo Clinic) diagnosed between 2003 and 2011 retrospectively identified for inclusion in the analysis.
Prognostic variables	Severe functional tricuspid regurgitation Moderate functional tricuspid regurgitation Trivial functional tricuspid regurgitation (referent) Functional tricuspid regurgitation was diagnosed by tricuspid valve examination excluding any structural leaflet abnormality and was graded according to American Society of Echocardiography guidelines as absent, trivial, mild, moderate, and severe.
Confounders	Cox proportional hazards regression models analysing the association of functional tricuspid regurgitation with mortality were adjusted for age, sex, ejection fraction, atrial fibrillation, E/e′, pulmonary hypertension and Charlson comorbidity index incrementally. Additional variables including either the MAGGIC score or degree of right ventricular dysfunction (normal, mild, moderate or severe) were further included in two different models. Both were extracted below. Note that various models with increasing numbers of confounders adjusted for are included in the report – the two models that adjusted for the most confounders have been extracted below.
Outcomes and effect sizes	**Mortality under medical management** **Model 1: HR 1.14 (95% CI 1.01 to 1.29) for moderate functional TR vs. trivial functional TR –** adjusted for age, sex, ejection fraction, atrial fibrillation, E/e′, pulmonary hypertension, Charlson comorbidity index and MAGGIC score

Reference	Benfari 2019[16]
	Model 1: HR 1.35 (95% CI 1.11 to 1.63) for severe functional TR vs. trivial functional TR – adjusted for age, sex, ejection fraction, atrial fibrillation, E/e′, pulmonary hypertension, Charlson comorbidity index and MAGGIC score **Model 2: HR 1.17 (95% CI 1.07 to 1.28) for moderate functional TR vs. trivial functional TR –** adjusted for age, sex, ejection fraction, atrial fibrillation, E/e′, pulmonary hypertension, Charlson comorbidity index and right ventricular dysfunction degree **Model 2: HR 1.41 (95% CI 1.25 to 1.61) for severe functional TR vs. trivial functional TR –** adjusted for age, sex, ejection fraction, atrial fibrillation, E/e′, pulmonary hypertension, Charlson comorbidity index and right ventricular dysfunction degree Patients who underwent defibrillator implantation, left ventricular assistant device implantation or cardiac transplantation were censored at the time of these procedures. Five-year survival under medical management was 68±1% for trivial, 45±2% for moderate and 34±4% for severe functional TR; at 10 years, survival was 46±2%, 22±3%, and 14±4%, respectively. Number of events were reported to be 1,795, 1,371 and 502 for trivial, moderate and severe functional TR, respectively. Median follow-up: 4.02 (0.95-7.12) years.
Comments, risk of bias and indirectness	Risk of bias: <u>For moderate functional TR as prognostic factor</u> 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 *Note: the same risk of bias rating applies to both models reported for this prognostic factor* <u>For severe functional TR as prognostic factor</u>

Reference	Benfari 2019[16]	
	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

Note: the same risk of bias rating applies to both models reported for this prognostic factor

Indirectness:

<u>For moderate functional TR as prognostic factor</u>

- Prognostic factor indirectness – includes moderate severity tricuspid regurgitation with or without symptoms, whereas in protocol ideally aimed to look at moderate + symptomatic and moderate + asymptomatic as separate prognostic factors
- Confounders – though left ventricular ejection fraction and age have been included in the multivariate analysis, the remaining factors listed in the protocol as important confounders (stroke volume index, coexistent second heart valve disease, coexistent coronary disease and frailty) have not been directly adjusted for, though may have been partially captured in one of the risk scores that was included in the multivariable analyses (downgraded for this in risk of bias so not downgraded further for indirectness).

<u>For severe functional TR as prognostic factor</u>

- Confounders – though left ventricular ejection fraction and age have been included in the multivariate analysis, the remaining factors listed in the protocol as important confounders (stroke volume index, coexistent second heart valve disease, coexistent coronary disease and frailty) have not been directly adjusted for, though may have been partially captured in one of the risk scores that was included in the multivariable analyses (downgraded for this in risk of bias so not downgraded further for indirectness).

Reference	Topilsky 2018[135]
Study type and analysis	Retrospective cohort study Cox proportional hazards models Israel and USA
Number of participants and characteristics	N=291 Effective regurgitant orifice area ≥0.4 cm^2 (severe), n=82 Effective regurgitant orifice area <0.4 cm^2 (trivial, mild or moderate), n=209 Study population is those with a diagnosis of functional tricuspid regurgitation (TR) due to systolic left ventricular dysfunction. **Inclusion criteria:** Diagnosis of functional TR ranging from trivial to severe; systolic dysfunction (ejection fraction <50%); absence of other organic valve disease; absence of prior valve surgery. **Exclusion criteria:** Congenital TR (any congenital heart disease resulting in TR, including atrial septal defect); organic associated TR (not due to congenital disease and associated with structural tricuspid disease); TR associated with other valve disease (TR neither congenital nor organic and occurring in patients with valve prostheses, valve repair, any degree of mitral stenosis or any other native organic valve disease of at least moderate degree; normal systolic function (ejection fraction ≥50%. **Values listed below are presented as mean (SD) or number (%)** **Patient characteristics:** **<u>Effective regurgitant orifice area ≥0.4 cm^2 (severe)</u>** • Age: 69.3 (14) years • Male/female: 61/21 (74%/26%) • Systolic blood pressure: 117 (19) mmHg • Diastolic blood pressure: 69 (12) mmHg • Heart rate: 78 (17) bpm

Reference	Topilsky 2018[135]

	• Atrial fibrillation, 38 (46%)
	• Cerebrovascular accident, 12 (15%)
	• Ischaemic heart disease, 53 (64%)
	• Chronic obstructive pulmonary disease, 16 (19%)
	• Hypertension, 45 (55%)
	• Diabetes, 14 (17%)
	• Comorbidity index: 5.2 (2.5)
	• Medication:
	  ○ Furosemide, 82 (100%)
	  ○ Spironolactone, 19 (23%)
	  ○ ACE inhibitors, 82 (100%)
	  ○ Beta-blockers, 82 (100%)
	• Systolic murmur, 63 (77%)
	• NYHA class III-IV, 51 (62%)
	• Right heart failure, 40 (49%)
	• Renal dysfunction, 29 (35%)
	• Liver dysfunction, 18 (22%)
	• Elevated jugular venous pressure, 48 (58%)
	• Hepatojugular reflux, 31 (38%)
	• Oedema, 53 (65%)
	
	• LV end-diastolic diameter: 55.9 (8.0) mm
	• LV end-systolic diameter: 46.3 (8.0) mm
	• Ejection fraction: 31.0 (10.0)%
	• Ejection fraction quinines: 36.2 (12.0)%
	• Left atrium volume index: 65 (27) ml/m^2
	• Cardiac index: 2.3 (0.6) L/min/m^2
	• E-wave velocity: 1.00 (0.30) m/s
	• Deceleration time: 157 (38) ms
	• Functional mitral regurgitation ≥moderate, 13 (16%)

Reference	Topilsky 2018[135]

	• Mitral regurgitation effective regurgitant orifice: 0.13 (0.02) cm^2
	• Right ventricle enlarged, 62 (75%)
	• Right ventricle enlarged ≥moderate, 36 (44%)
	• Right ventricle dysfunction ≥moderate, 37 (45%)
	• Right ventricle fractional area change: 36.4 (5.0)
	• Right ventricular index of myocardial performance: 0.48 (0.20)
	• Right atrium enlarged, 63 (77%)
	• Right atrium pressure: 16.6 (4.0)%
	• Systolic pulmonary pressure: 57.3 (14.0) mmHg
	• Vena contracta: 8.9 (1.4) mm
	• Hepatic vein flow reversal: 48 (58%)
	• TR effective regurgitant orifice: 0.68 (0.20) cm^2
	• TR regurgitant volume: 58.8 (26.0) ml/beat
	
	Effective regurgitant orifice area <0.4 cm^2 (trivial, mild or moderate)
	• Age: 70.13 (11) years
	• Male/female: 138/71 (66%/34%)
	• Systolic blood pressure: 125.70 (22.07) mmHg
	• Diastolic blood pressure: 71.00 (12.71) mmHg
	• Heart rate: 77.00 (16.71) bpm
	• Atrial fibrillation, 47 (23%)
	• Cerebrovascular accident, 16 (8%)
	• Ischaemic heart disease, 142 (68%)
	• Chronic obstructive pulmonary disease, 39 (19%)
	• Hypertension, 102 (49%)
	• Diabetes, 61 (29%)
	• Comorbidity index: 5.10 (2.93)
	• Medication:
	  ○ Furosemide, 184 (88%)
	  ○ Spironolactone, 26 (12%)

Reference	Topilsky 2018[135]
	○ ACE inhibitors, 186 (89%) ○ Beta-blockers, 150 (72%) • Systolic murmur, 113 (54%) • NYHA class III-IV, 104 (50%) • Right heart failure, 41 (20%) • Renal dysfunction, 46 (22%) • Liver dysfunction, 8 (4%) • Elevated jugular venous pressure, 51 (24%) • Hepatojugular reflux, 16 (8%) • Oedema, 78 (37%) • LV end-diastolic diameter: 59.14 (9.51) mm • LV end-systolic diameter: 48.60 (10.59) mm • Ejection fraction: 31.40 (9.73)% • Ejection fraction quinines: 36.95 (12.18)% • Left atrium volume index: 53.70 (19.81) ml/m^2 • Cardiac index: 2.63 (0.67) L/min/m^2 • E-wave velocity: 0.94 (0.27) m/s • Deceleration time: 166.50 (52.87) ms • Functional mitral regurgitation ≥moderate, 31 (15%) • Mitral regurgitation effective regurgitant orifice: 0.11 (0.02) cm^2 • Right ventricle enlarged, 69 (33%) • Right ventricle enlarged ≥moderate, 54 (26%) • Right ventricle dysfunction ≥moderate, 72 (34%) • Right ventricle fractional area change: 38.35 (4.96) • Right ventricular index of myocardial performance: 0.60 (0.27) • Right atrium enlarged, 88 (42%) • Right atrium pressure: 13.18 (4.47)% • Systolic pulmonary pressure: 55.93 (13.88) mmHg • Vena contracta: 2.21 (1.13) mm

Reference	Topilsky 2018[135]
	• Hepatic vein flow reversal: 40 (19%) • TR effective regurgitant orifice: 0.10 (0.15) cm^2 • TR regurgitant volume: 10.43 (15.66) ml/beat **Population source:** For mild-severe TR patients, consecutive patients matching inclusion criteria with TR quantification performed between 1995 and 2005. Unclear whether at a single centre or multiple. Note that for trivial TR cases, patients were randomly selected from the desired group of patients with trivial TR, with similar eligibility criteria and systolic dysfunction, in the computerised Mayo Clinic echocardiography database. Mild-severe TR patients and trivial TR patients were therefore comparable in terms of other independent determinants of outcome. Pre-defined matching parameters were age (within 5 years), gender, ejection fraction (within 5%), exact year of diagnosis, comorbidity index (within 0.2) and systolic TR peak velocity (within 0.2 m/s).
Prognostic variables	Effective regurgitant orifice area ≥0.4 cm^2 (severe) Effective regurgitant orifice area <0.4 cm^2 (trivial, mild or moderate) (referent) Separated into severity categories based on echocardiography measurements of effective regurgitant orifice area (ERO) as follows: trivial TR, ERO =0 cm^2; mild-moderate TR, ERO >0 and <0.4 cm^2; and severe TR, ERO ≥0.4 cm^2.
Confounders	Multivariate models included the following variables: ERO ≥0.4 cm^2, age, sex, comorbidity index, left ventricular ejection fraction, atrial fibrillation, left atrial size, right ventricular dysfunction ≥moderate, renal failure and right ventricular systolic pressure. Note that more than one multivariate model is described, adjusting for different numbers of variables. The model that has adjusted for the highest number of variables has been extracted in the results.
Outcomes and effect sizes	**All-cause mortality – medically managed and censored at time of cardiac surgery** **HR 1.80 (1.16 to 2.80) for effective regurgitant orifice area ≥0.4 cm^2 (severe) vs. <0.4 cm^2 (trivial, mild or moderate)** There were 167 deaths during follow-up after diagnosis. Survival was 78±2%, 54±3% and 41±4% at 1, 3 and 5 years, respectively. Deaths were due to cardiac causes (n=74), cancer (n=20), stroke (n=20), infection (n=19), advanced liver disease (n=18), advanced dementia (n=11) and unknown (n=5). In trivial, mild-moderate and severe TR groups, 5-year survival was 47±5%, 46±7% and 27±5%, respectively. Management of TR following diagnosis was medical only in 282 patients (97%) and was medical followed by surgery in 9 patients (3%). Surgery in all patients was due to severe right heart failure symptoms and TR was severe at the time of operation in all patients. Valve repair was performed in 8 patients while replacement with a biological valve was performed in 1 patient. Median follow-up reported as 1.9 (0.5-6.6) years. Likely to be median and range but is unclear.

Reference	Topilsky 2018[135]
Comments, risk of bias and indirectness	Risk of bias: 1. Study participation HIGH 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement LOW 5. Study confounding HIGH 6. Statistical analysis HIGH 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH Indirectness: • Confounders – though some multivariate analysis has been performed, only age and ejection fraction pre-specified in the protocol were included in this analysis. The remaining pre-specified factors were not included (coronary disease, stroke volume index, frailty and coexistent second heart valve disease) (downgraded for this in risk of bias so not downgraded further for indirectness). Others may have been captured by the use of the comorbidity index in the adjusted analysis, but not all of them would have been.

Appendix E – Forest plots

E.1 Aortic stenosis

Figure 2: Symptomatic (NYHA class III-IV) versus asymptomatic (NYHA class I-II) in moderate AS

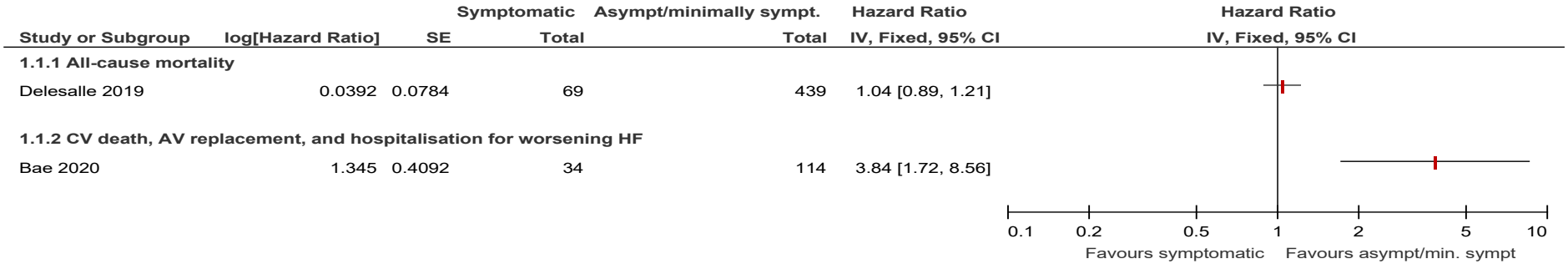
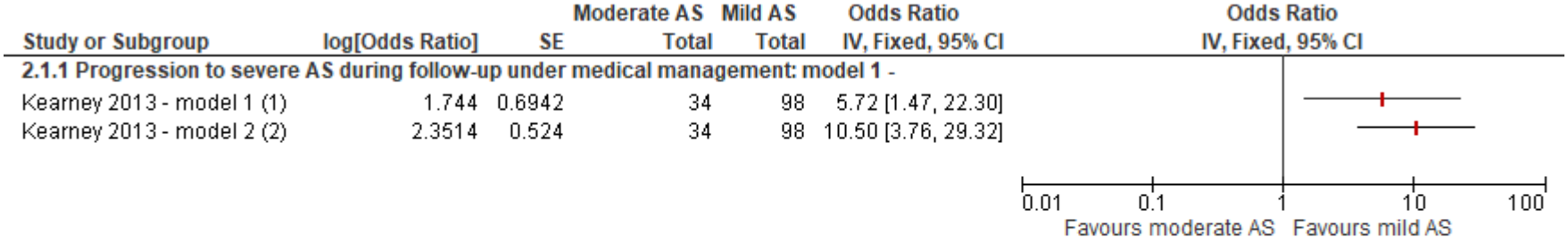


Figure 3: Moderate AS (aortic valve area 1.0-1.5 cm² or mean gradient 25-40 mmHg) versus mild AS (aortic valve area >1.5 cm² or mean gradient <25 mmHg) in mild-moderate AS with or without symptoms



Footnotes

(1) Adjusted for duration of follow-up, history of myocardial infarction, mean aortic valve gradient and aortic valve calcification

(2) Adjusted for duration of follow-up, history of myocardial infarction and mean aortic valve gradient

Figure 4: Moderate asymptomatic AS (peak aortic jet velocity ≥3 m/s) versus mild asymptomatic AS (peak aortic jet velocity <3 m/s) in asymptomatic mild-moderate AS initially medically managed

Study or Subgroup	log[Hazard Ratio]	SE	Moderate asympt. AS Total	Mild asympt. AS Total	Hazard Ratio IV, Fixed, 95% CI
3.1.1 Aortic valve replacement or death					
Rosenhek 2004	0.47	0.2217	120	56	1.60 [1.04, 2.47]

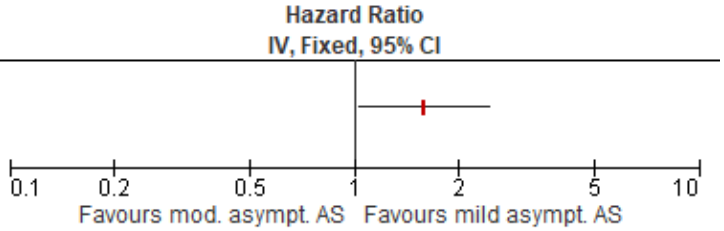


Figure 5: Severe AS (valve area <1.0 cm^2) vs. mild-moderate AS (valve area ≥1.0 cm^2) in mild-severe AS under medical management with or without symptoms

Study or Subgroup	log[Hazard Ratio]	SE	Severe AS Total	Mild-moderate AS Total	Hazard Ratio IV, Fixed, 95% CI
4.1.1 Mortality					
Malouf 2012	0.5933	0.214	96	264	1.81 [1.19, 2.75]
4.1.2 Aortic valve replacement					
Malouf 2012	1.0296	0.2855	96	264	2.80 [1.60, 4.90]
4.1.3 Congestive heart failure development under medical management					
Malouf 2012	0.8329	0.2911	96	264	2.30 [1.30, 4.07]

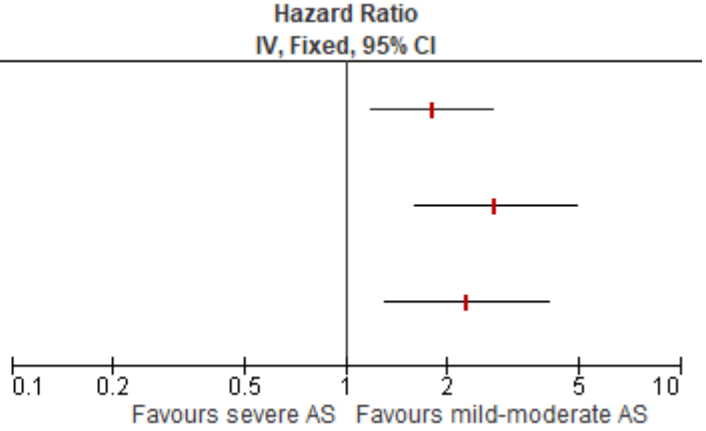
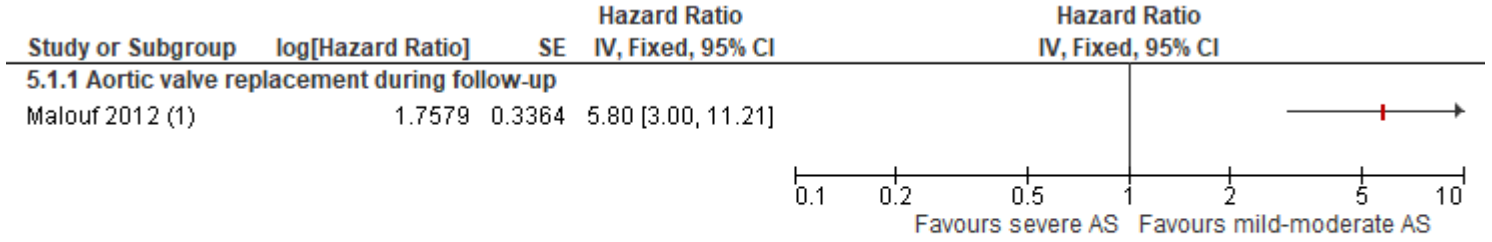


Figure 6: Severe AS (mean gradient ≥40 mmHg) vs. mild-moderate AS (<40 mmHg) in mild-severe AS initially medically managed with or without symptoms



Footnotes
(1) Number in each group not reported

Figure 7: Low-gradient low-flow severe AS (aortic valve area <1 cm^2, indexed valve area <0.6 cm^2, mean gradient <40 mmHg and stroke volume index <35 ml/m^2) versus mild-moderate AS (aortic valve area ≥1.0 cm^2 or indexed valve area ≥0.6 cm^2 and mean gradient <40 mmHg) in mild-severe AS under medical management with or without symptoms

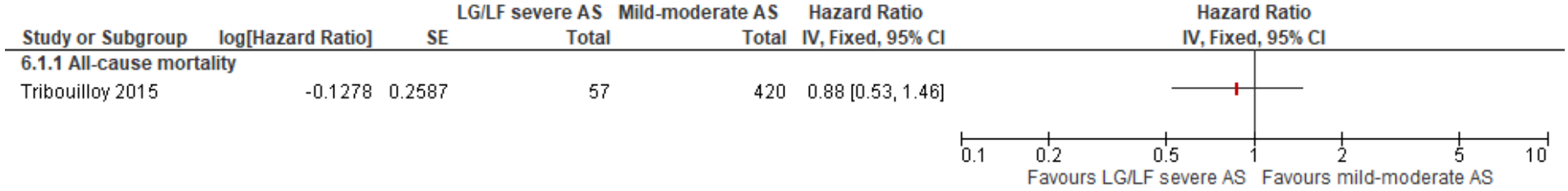


Figure 8: Low-gradient normal-flow severe AS (aortic valve area <1 cm^2, indexed valve area <0.6 cm^2, mean gradient <40 mmHg and stroke volume index ≥35 ml/m^2) versus mild-moderate AS (aortic valve area ≥1.0 cm^2 or indexed valve area ≥0.6 cm^2 and mean gradient <40 mmHg) in mild-severe AS under medical management with or without symptoms

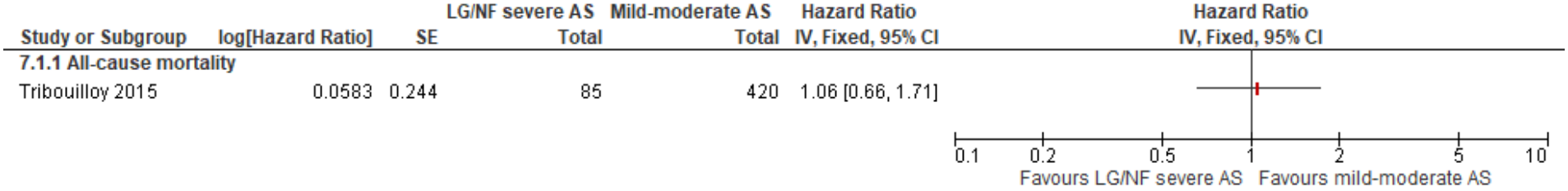
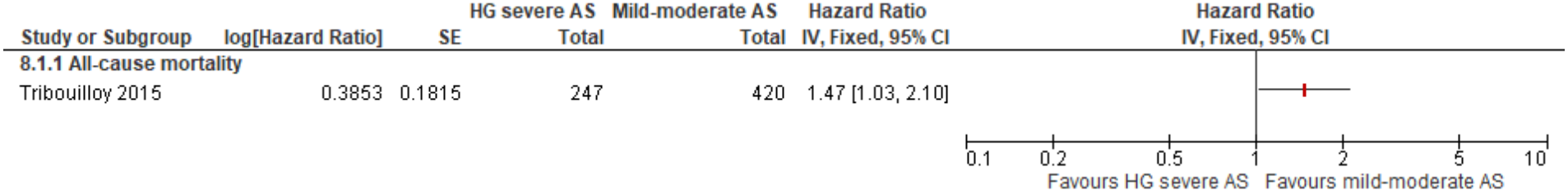


Figure 9: High-gradient severe AS (aortic valve area <1 cm^2, indexed valve area <0.6 cm^2, mean gradient ≥40 mmHg) versus mild-moderate AS (aortic valve area ≥1.0 cm^2 or indexed valve area ≥0.6 cm^2 and mean gradient <40 mmHg) in mild-severe AS under medical management with or without symptoms



E.2 Aortic regurgitation

Figure 10: QASE-severe grade (regurgitant volume ≥60 ml/beat or effective regurgitant orifice area ≥30 mm^2) versus QASE-mild grade (regurgitant volume <30 ml/beat and effective regurgitant orifice area <10 mm^2) in asymptomatic mild-severe AR under initial conservative management

Study or Subgroup	log[Hazard Ratio]	SE	Severe asymptomatic AR Total	Mild asymptomatic AR Total	Hazard Ratio IV, Fixed, 95% CI
9.1.1 Mortality under conservative managment					
Detaint 2008	1.411	0.5482	93	51	4.10 [1.40, 12.01]
9.1.2 Mortality or aortic valve replacement for AR					
Detaint 2008	2.5572	0.4443	93	51	12.90 [5.40, 30.82]

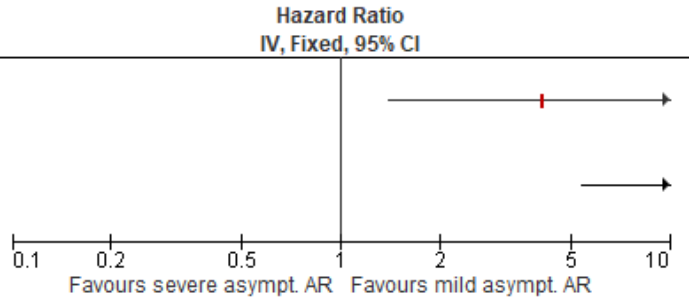
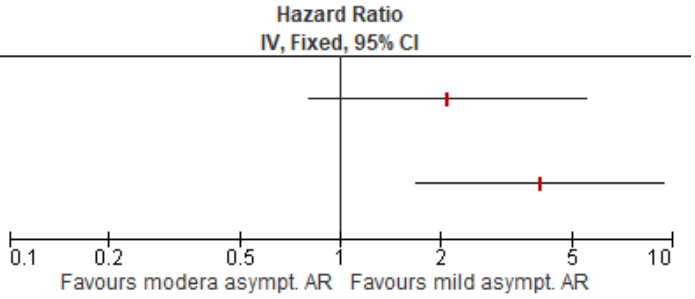


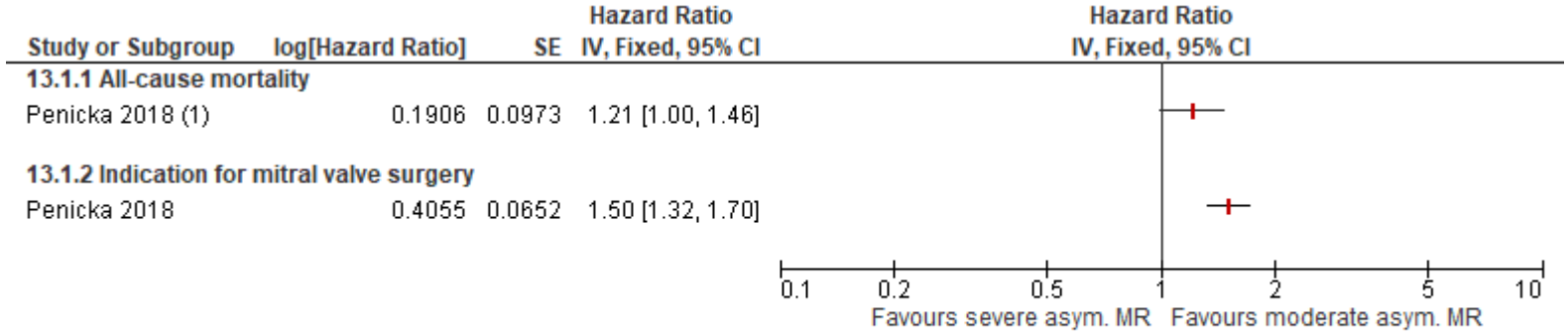
Figure 11: QASE-moderate grade (regurgitant volume ≥30 ml/beat or effective regurgitant orifice area ≥10 mm^2, but not reaching severe thresholds) versus QASE-mild grade (regurgitant volume <30 ml/beat and effective regurgitant orifice area <10 mm^2) in asymptomatic mild-severe AR under initial conservative management

Study or Subgroup	log[Hazard Ratio]	SE	Moderate asymptomatic AR Total	Mild asymptomatic AR Total	Hazard Ratio IV, Fixed, 95% CI
10.1.1 Mortality under conservative managment					
Detaint 2008	0.7419	0.4924	107	51	2.10 [0.80, 5.51]
10.1.2 Mortality or aortic valve replacement for AR					
Detaint 2008	1.3863	0.4366	107	51	4.00 [1.70, 9.41]



E.3 Mitral regurgitation

Figure 12: Severe asymptomatic MR (regurgitant volume ≥60 ml) versus moderate asymptomatic MR (regurgitant volume 30-59 ml) in asymptomatic moderate-severe MR



Footnotes
(1) Numbers in each group not reported

Figure 13: Severe asymptomatic MR (effective regurgitant orifice area ≥40 mm^2) versus mild asymptomatic MR (effective regurgitant orifice area <20 mm^2) in asymptomatic mild-severe MR under medical management

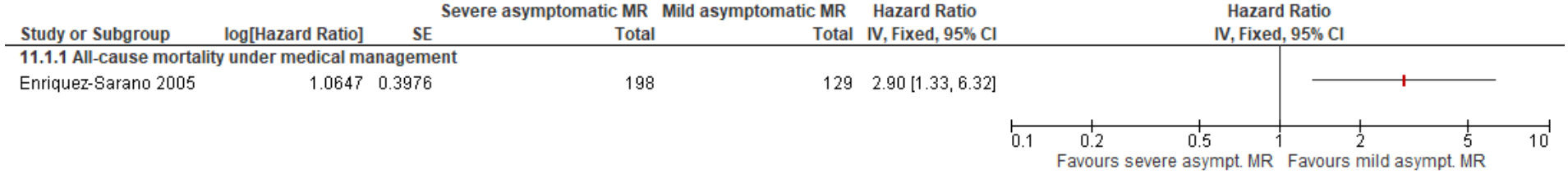
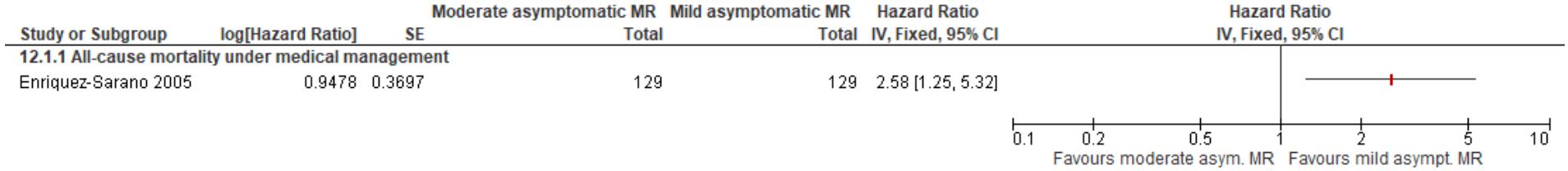
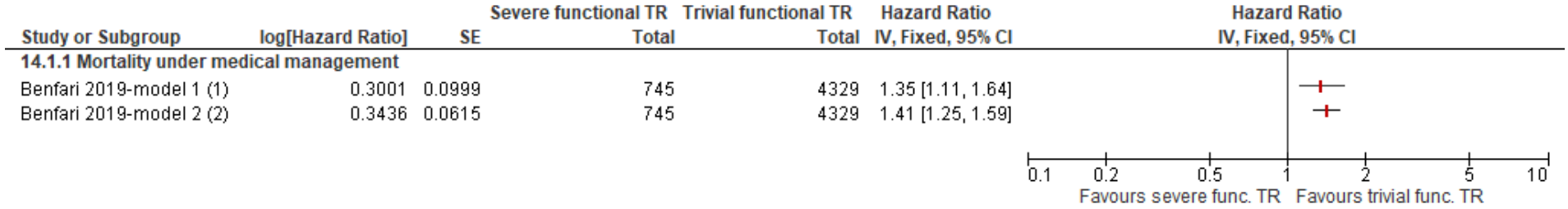


Figure 14: Moderate asymptomatic MR (effective regurgitant orifice area 20-39 mm^2) versus mild asymptomatic MR (effective regurgitant orifice area <20 mm^2) in asymptomatic mild-severe MR under medical management



E.4 Tricuspid regurgitation

Figure 15: Severe functional TR versus trivial functional TR (graded according to American Society of Echocardiography guidelines) in trivial-severe symptomatic functional TR

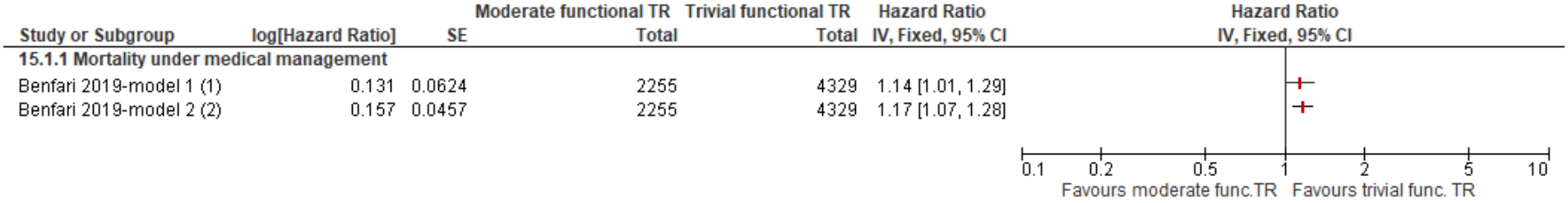


Footnotes

(1) Adjusted for age, sex, ejection fraction, atrial fibrillation, E/e', pulmonary hypertension, Charlson comorbidity index and MAGGIC score

(2) Adjusted for age, sex, ejection fraction, atrial fibrillation, E/e', pulmonary hypertension, Charlson comorbidity index and right ventricular dysfunction degree

Figure 16: Moderate functional TR versus trivial functional TR (graded according to American Society of Echocardiography guidelines) in trivial-severe symptomatic functional TR

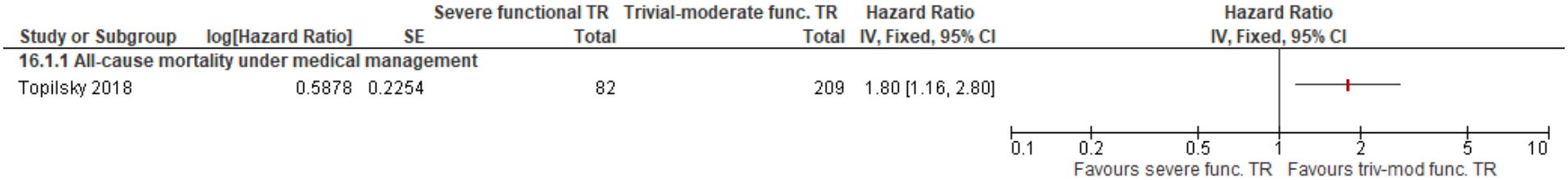


Footnotes

(1) Adjusted for age, sex, ejection fraction, atrial fibrillation, E/e', pulmonary hypertension, Charlson comorbidity index and MAGGIC score

(2) Adjusted for age, sex, ejection fraction, atrial fibrillation, E/e', pulmonary hypertension, Charlson comorbidity index and right ventricular dysfunction degree

Figure 17: Severe functional TR (effective regurgitant orifice area ≥0.4 cm^2) vs. trivial, mild or moderate functional TR (effective regurgitant orifice area <0.4 cm^2) in trivial-severe functional TR due to systolic left ventricular dysfunction with or without symptoms



Appendix F – GRADE tables

F.1 Aortic stenosis

Table 21: Clinical evidence profile: symptomatic versus asymptomatic in moderate AS

Quality assessment							No patients		Effect	Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations (including publication bias where possible)	Symptomatic	Asymptomatic/ minimally symptomatic	Relative effect (95% CI)	
All-cause mortality (adjusted HR) – symptomatic (NYHA class III or IV) vs. asymptomatic/minimally symptomatic (NYHA class I-II) moderate AS (moderate AS; mean age: 75 (11) years; medically managed initially and adjusted for aortic valve replacement in analysis if performed). Follow-up median 47 months.										
1	Cohort study	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	69	439	Adjusted HR 1.04 (0.89 to 1.21)[4]	VERY LOW
CV death, AV replacement, and hospitalisation for worsening HF - Moderate AS: symptomatic vs asymptomatic (follow-up mean 5.6 years)										
1	Cohort study	very serious[1]	no serious inconsistency	serious[2]	No serious imprecision	none	34	114	Adjusted HR 3.84 (1.72 to 5.86)[5]	VERY LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2]Prognostic factor indirectness - prognostic groups are split into asymptomatic/minimally symptomatic and symptomatic groups based on NYHA classes of I-II and III-IV, respectively. Ideally would be interested in asymptomatic vs. any symptoms in line with the protocol.
[3]95% CIs cross null line
[4]Methods: multivariable analysis, including some but not all variables pre-specified in the protocol. The following variables were included: age, sex, body surface area, New York Heart Association class, prior atrial fibrillation, mean transaortic pressure gradient, left ventricular ejection fraction, history of myocardial infarction, moderate-severe aortic valve calcification, Charlson comorbidity index and aortic valve replacement
[5] Methods: multivariable analysis, including some but not all variables prespecified in the protocol. The following variables were included: Diabetes, AV area < 1.25 cm^2, moderate or moderate-to-severe MR, LVEF, E/e', LVESD, IVRT, NT pro-BNP, creatinine, very high CV risk

Table 22: Clinical evidence profile: moderate versus mild AS in those with or without symptoms

Quality assessment							No of patients		Effect	Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations (including publication bias where possible)	Moderate AS	Mild AS	Relative effect (95% CI)	
Progression to severe AS during follow-up (adjusted OR) – moderate AS (aortic valve area 1.0-1.5 cm^2 or mean gradient 25-40 mmHg) vs. mild AS (aortic valve area >1.5 cm^2 or mean gradient <25 mmHg) (mild-moderate AS; mean age 73 (6) years[1]; medically managed initially and follow-up censored at time of aortic valve replacement or death). Follow-up mean 6.5 years.										
1	Cohort study	very serious[2]	no serious inconsistency	very serious[3]	no serious imprecision	none	34	98	Model 1: Adjusted OR 5.72 (1.47 to 22.3)[4] Model 2: Adjusted OR 10.5 (3.76 to 29.32)[5]	VERY LOW

[1]Note: this mean age includes n=15 patients with severe AS that were not included in the analysis extracted, as a separate mean age for the mild-moderate population was not provided
[2]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[3]Prognostic factor indirectness: moderate severity valve disease with/without symptoms used as prognostic factor, whereas ideally the aim was to look at moderate symptomatic and moderate asymptomatic valve disease as separate prognostic factors; outcome indirectness: progression to severe valve disease is not listed as an outcome in the protocol but has been included as indirect evidence for need for intervention due to limited other available evidence. However, the study defines indication for intervention as severe + symptomatic and is therefore indirect as there is no information as to the symptomatic status of patients and therefore the requirement for intervention.
[4]Methods: multivariable analysis, not including any of those pre-specified in the protocol. The following variables were included: duration of follow-up, history of myocardial infarction, mean aortic valve gradient and aortic valve calcification (note only 62% had complete data for this variable).
[5]Methods: multivariable analysis, not including any of those pre-specified in the protocol. The following variables were included: duration of follow-up, history of myocardial infarction and mean aortic valve gradient.

Table 23: Clinical evidence profile: moderate AS versus mild-in asymptomatic AS

Quality assessment							No of patients		Effect	Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations (including publication bias where possible)	Moderate AS	Mild AS	Relative effect (95% CI)	

Aortic valve replacement or death (adjusted HR) – moderate asymptomatic AS (peak aortic jet velocity ≥3 m/s) vs. mild asymptomatic AS (peak aortic jet velocity <3 m/s) (asymptomatic mild-moderate AS; mean age 58 (19) years; medically managed initially as aortic valve replacement forms part of the outcome). Median follow-up 55 months.										
1	Cohort study	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	120	56	Adjusted HR 1.6 (1.04 to 2.80)[2]	LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2]Methods: multivariable analysis, including some but not all variables pre-specified in the protocol. The following variables were included: age ≥50 years, gender, coronary artery disease, hypertension, diabetes, hypercholesterolaemia, aortic valve peak velocity ≥3 m/s (moderate) and aortic valve calcification score 3 or 4. *Result listed as RR in study table but methods state Cox proportional hazards used, so reported as HR here.*

Table 24: Clinical evidence profile: severe AS (valve area <1.0 cm2) vs. mild-moderate AS (valve area ≥1.0 cm2) in those with or without symptoms

Quality assessment							No of patients		Effect	Quality
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations (including publication bias where possible)**	**Severe AS**	**Mild-moderate AS**	**Relative effect (95% CI)**	
Mortality (adjusted HR) – severe AS based on valve area (<1.0 cm^2) vs. mild-moderate AS (aortic valve area ≥1.0 cm^2) (mild-severe AS; mean age 74 (14) years for whole study – mean age for prognostic factor and referent groups was 77.0 and 72.3 years, respectively; medically managed initially and censored at time of aortic valve replacement). Follow-up mean 7.5 years.										
1	Cohort study	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	96	264	Adjusted HR 1.81 (1.19 to 2.75)[2]	LOW
Congestive heart failure development (adjusted HR) – severe AS based on valve area (<1.0 cm^2) vs. mild-moderate AS (aortic valve area ≥1.0 cm^2) (mild-severe AS; mean age 74 (14) years for whole study – mean age for prognostic factor and referent groups was 77.0 and 72.3 years, respectively; medically managed initially and censored at time of aortic valve replacement). Follow-up mean 7.5 years.										
1	Cohort study	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	96	264	Adjusted HR 2.3 (1.3 to 4.07)[3]	LOW
Aortic valve replacement after initial medical management (adjusted HR) – severe AS based on valve area (<1.0 cm^2) vs. mild-moderate AS (aortic valve area ≥1.0 cm^2) (mild-severe AS; mean age 74 (14) years for whole study – mean age for prognostic factor and referent groups was 77.0 and 72.3 years, respectively; medically managed initially and censored at time of aortic valve replacement). Follow-up mean 7.5 years.										

1	Cohort study	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	96	264	Adjusted HR 2.8 (1.6 to 4.9)[4]	LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2]Methods: multivariable analysis, including some but not all variables pre-specified in the protocol. The following variables were included: valve area <1.0 cm^2, age, sex, comorbidity score and atrial fibrillation. Possibly also included ejection fraction and class III-IV symptoms, but unclear. May have been others included but not well reported.
[3]Methods: multivariable analysis, including some but not all variables pre-specified in the protocol. The following variables were included: valve area <1.0 cm^2, age, comorbidity score and atrial fibrillation. Possibly also included ejection fraction and class III-IV symptoms, but unclear. May have been others included but not well reported.
[4]Methods: multivariable analysis, including some but not all variables pre-specified in the protocol. The following variables were included: valve area <1.0 cm^2, age, sex, comorbidity score, atrial fibrillation, ejection fraction and class III-IV symptoms. May have been others included but not well reported.

Table 25: Clinical evidence profile: severe AS (mean gradient ≥40 mmHg) vs. mild-moderate AS (<40 mmHg) in those with or without symptoms

Quality assessment							No of patients		Effect	Quality
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations (including publication bias where possible)**	**Severe AS**	**Mild-moderate AS**	**Relative effect (95% CI)**	
Aortic valve replacement during follow-up (adjusted HR) – severe AS based on mean gradient (≥40 mmHg) vs. mild-moderate AS (mean gradient <40 mmHg) (mild-severe AS; mean age 74 (14) years for whole cohort; medically managed initially). Follow-up mean 7.5 years.										
1	Cohort study	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	360		Adjusted HR 5.8 (3 to 11.21)[2]	LOW

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Methods: multivariable analysis, including some but not all variables pre-specified in the protocol. The following variables were included: mean gradient ≥40 mmHg, age, sex, comorbidity score, atrial fibrillation, ejection fraction and class III-IV symptoms. May have been others included but not well reported.

Table 26: Clinical evidence profile: low-gradient low-flow severe AS versus mild-moderate AS in those with or without symptoms

Quality assessment	No of patients	Effect	Quality

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations (including publication bias where possible)	LG/LF severe AS	Mild-moderate AS	Relative effect (95% CI)	
All-cause mortality (adjusted HR) – low-gradient low-flow severe AS (aortic valve area <1 cm^2, indexed valve area <0.6 cm^2, mean gradient <40 mmHg and stroke volume index <35 ml/m^2 vs. mild-moderate AS (aortic valve area ≥1.0 cm^2 or indexed valve area ≥0.6 cm^2 and mean gradient <40 mmHg) (mild-severe AS; mean age 75 (12) years for whole study – median age for the prognostic factor and referent groups was 78.5 and 76.9 years, respectively; medically managed initially and censored at time of cardiac surgery). Median follow-up 22.8 months.										
1	Cohort study	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	57	420	Adjusted HR 0.88 (0.53 to 1.46)[4]	VERY LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2]Prognostic factor indirectness - severe AS is split into three different groups that are each compared with the same referent of mild-moderate AS, rather than looking at severe AS as a whole as a prognostic factor as specified in the protocol.
[3]95% CIs cross null line
[4]Methods: multivariable analysis, including some but not all variables pre-specified in the protocol. The following variables were included: severity classification, age, sex body surface area, Charlson comorbidity index, symptoms at baseline, coronary artery disease, history of atrial fibrillation and ejection fraction.

Table 27: Clinical evidence profile: low-gradient normal-flow severe versus mild-moderate AS in those with or without symptoms

Quality assessment							No of patients		Effect	Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations (including publication bias where possible)	LG/NF severe AS	Mild-moderate AS	Relative effect (95% CI)	
All-cause mortality (adjusted HR) – low-gradient normal-flow severe AS (aortic valve area <1 cm^2, indexed valve area <0.6 cm^2, mean gradient <40 mmHg and stroke volume index ≥35 ml/m^2) vs. mild-moderate AS (aortic valve area ≥1.0 cm^2 or indexed valve area ≥0.6 cm^2 and mean gradient <40 mmHg) (mild-severe AS; mean age 75 (12) years for whole study – median age for the prognostic factor and referent groups was 79.3 and 76.9 years, respectively; medically managed initially and censored at time of cardiac surgery). Median follow-up 22.8 months.										
1	Cohort study	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	65	420	Adjusted HR 1.06 (0.66 to 1.71)[4]	VERY LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2]Prognostic factor indirectness - severe AS is split into three different groups that are each compared with the same referent of mild-moderate AS, rather than looking at severe AS as a whole as a prognostic factor as specified in the protocol.
[3]95% CIs cross null line
[4]Methods: multivariable analysis, including some but not all variables pre-specified in the protocol. The following variables were included: severity classification, age, sex, body surface area, Charlson comorbidity index, symptoms at baseline, coronary artery disease, history of atrial fibrillation and ejection fraction.

Table 28: Clinical evidence profile: high-gradient severe AS versus mild-moderate AS in those with or without symptoms

Quality assessment							No of patients		Effect	Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations (including publication bias where possible)	HG severe AS	Mild-moderate AS	Relative effect (95% CI)	
All-cause mortality (adjusted HR) – high-gradient severe AS (aortic valve area <1 cm^2, indexed valve area <0.6 cm^2, mean gradient ≥40 mmHg) vs. mild-moderate AS (aortic valve area ≥1.0 cm^2 or indexed valve area ≥0.6 cm^2 and mean gradient <40 mmHg) (mild-severe AS; mean age 75 (12) years for whole study – median age for the prognostic factor and referent groups was 76.9 and 76.9 years, respectively; medically managed initially and censored at time of cardiac surgery). Median follow-up 22.8 months.										
1	Cohort study	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	247	420	Adjusted HR 1.47 (1.03 to 2.1)[3]	VERY LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2]Prognostic factor indirectness - severe AS is split into three different groups that are each compared with the same referent of mild-moderate AS, rather than looking at severe AS as a whole as a prognostic factor as specified in the protocol.
[3]Methods: multivariable analysis, including some but not all variables pre-specified in the protocol. The following variables were included: severity classification, age, sex, body surface area, Charlson comorbidity index, symptoms at baseline, coronary artery disease, history of atrial fibrillation and ejection fraction.

F.2 Aortic regurgitation

Table 29: Clinical evidence profile: QASE-severe versus QASE-mild grade in asymptomatic AR

Quality assessment							No of patients		Effect	Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations (including publication bias where possible)	Severe asymptomatic	Mild asymptomatic	Relative effect (95% CI)	

Mortality (adjusted HR) – QASE[1]-severe grade (regurgitant volume ≥60 ml/beat or effective regurgitant orifice area ≥30 mm^2) vs. QASE[1]-mild grade (regurgitant volume <30 ml/beat and effective regurgitant orifice area <10 mm^2) (asymptomatic mild-severe AR; mean age 60 (17) years for whole cohort – mean age for prognostic factor and referent groups was 58 and 62 years, respectively; medically managed initially). Follow-up mean 8.0 years.										
1	Cohort study	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	93	51	Adjusted HR 4.1 (1.4 to 12.01)[3]	LOW
Mortality or aortic valve replacement for AR (adjusted HR) – QASE[1]-severe grade (regurgitant volume ≥60 ml/beat or effective regurgitant orifice area ≥30 mm^2) vs. QASE[1]-mild grade (regurgitant volume <30 ml/beat and effective regurgitant orifice area <10 mm^2) (asymptomatic mild-severe AR; mean age 60 (17) years for whole cohort – mean age for prognostic factor and referent groups was 58 and 62 years, respectively; medically managed initially). Follow-up mean 8.0 years.										
1	Cohort study	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	93	51	Adjusted HR 12.9 (5.4 to 30.82)[4]	LOW

[1]QASE refers to the quantitative American Society of Echocardiography thresholds, which were used for AR grading
[2]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[3]Methods: multivariable analysis, including some but not all variables pre-specified in the protocol. The following variables were included: age, gender, AR quantitative classification, comorbidity score and ejection fraction.
[4]Methods: multivariable analysis, including some but not all variables pre-specified in the protocol. The following variables were included: age, gender, AR quantitative classification, end-systolic volume index and comorbidity index.

Table 30: Clinical evidence profile: QASE-moderate versus QASE-mild grade in asymptomatic AR

Quality assessment							No of patients		Effect	Quality
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations (including publication bias where possible)**	**Moderate asymptomatic**	**Mild asymptomatic**	**Relative effect (95% CI)**	
Mortality (adjusted HR) – QASE[1]-moderate grade (regurgitant volume ≥30 ml/beat or effective regurgitant orifice area ≥10 mm^2, but not reaching severe thresholds) vs. QASE[1]-mild grade (regurgitant volume <30 ml/beat and effective regurgitant orifice area <10 mm^2) (asymptomatic mild-severe AR; mean age 60 (17) years for whole cohort – mean age for prognostic factor and referent groups was 62 and 62 years, respectively; medically managed initially). Follow-up mean 8.0 years.										
1	Cohort study	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	107	51	Adjusted HR 2.1 (0.8 to 5.51)[4]	VERY LOW

Mortality or aortic valve replacement for AR (adjusted HR) – QASE[1]-moderate grade (regurgitant volume ≥30 ml/beat or effective regurgitant orifice area ≥10 mm^2, but not reaching severe thresholds) vs. QASE[1]-mild grade (regurgitant volume <30 ml/beat and effective regurgitant orifice area <10 mm^2) (asymptomatic mild-severe AR; mean age 60 (17) years for whole cohort – mean age for prognostic factor and referent groups was 62 and 62 years, respectively; medically managed initially). Follow-up mean 8.0 years.										
1	Cohort study	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	107	51	Adjusted HR 4 (1.7 to 9.41)[5]	LOW

[1]QASE refers to the quantitative American Society of Echocardiography thresholds, which were used for AR grading
[2]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[3]95% CIs cross null line
[4]Methods: multivariable analysis, including some but not all variables pre-specified in the protocol. The following variables were included: age, gender, AR quantitative classification, comorbidity score and ejection fraction.
[5]Methods: multivariable analysis, including some but not all variables pre-specified in the protocol. The following variables were included: age, gender, AR quantitative classification, end-systolic volume index and comorbidity index.

F.3 Mitral regurgitation

Table 31: Clinical evidence profile: severe versus moderate in asymptomatic MR

Quality assessment							No of patients		Effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Severe MR**	**Moderate MR**	**Relative effect (95% CI)**	
All-cause mortality - HR - adjusted for age, sex, and LVESD (follow-up median 5 years)										
1	Cohort study	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	258		HR 1.21 (1 to 1.46)[3]	⊕OOO VERY LOW
Indication for mitral valve surgery - HR - adjusted for age, sex, and LVESD (follow-up median 5 years)										
1	Cohort study	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	258		HR 1.5 (1.32 to 1.7)[3]	⊕⊕OO LOW

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] 95% CI crosses the null line
[3] Methods: multivariable analysis, including some but not all variables pre-specified in the protocol. The following variables were included: Age, sex, and LVESD on echo.

Table 32: Clinical evidence profile: severe versus mild in asymptomatic MR

Quality assessment							No of patients		Effect	Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations (including publication bias where possible)	Severe MR	Mild MR	Relative effect (95% CI)	
All-cause mortality (adjusted HR) – severe asymptomatic MR (effective regurgitant orifice area ≥40 mm^2) vs. mild asymptomatic MR (effective regurgitant orifice area <20 mm^2) (asymptomatic mild-severe MR; mean age 63 (14) years for whole cohort – mean age of prognostic factor and referent groups was 61 and 64 years, respectively; medically managed initially and censored at time of surgery). Mean follow-up 2.7 years.										
1	Cohort study	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	198	129	Adjusted HR 2.9 (1.33 to 6.32)[2]	LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2]Methods: multivariable analysis, including some but not all variables pre-specified in the protocol. The following variables were included: effective regurgitant orifice threshold grouping, age, sex, ejection fraction, presence of diabetes and presence of atrial fibrillation.

Table 33: Clinical evidence profile: moderate versus mild in asymptomatic MR

Quality assessment							No of patients		Effect	Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations (including publication bias where possible)	Moderate MR	Mild MR	Relative effect (95% CI)	
All-cause mortality (adjusted HR) – moderate asymptomatic MR (effective regurgitant orifice area 20-39 mm^2) vs. mild asymptomatic MR (effective regurgitant orifice area <20 mm^2) (asymptomatic mild-severe MR; mean age 63 (14) years for whole cohort – mean age of prognostic factor and referent groups was 65 and 64 years, respectively; medically managed initially and censored at time of surgery). Mean follow-up 2.7 years.										
1	Cohort study	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	129	129	Adjusted HR 2.58 (1.25 to 5.32)[2]	LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2]Methods: multivariable analysis, including some but not all variables pre-specified in the protocol. The following variables were included: effective regurgitant orifice threshold grouping, age, sex, ejection fraction, presence of diabetes and presence of atrial fibrillation.(regurgitant volume ≥60 ml) vs moderate MR (regurgitant volume 30-59 ml)

F.4 Tricuspid regurgitation

Table 34: Clinical evidence profile: severe versus trivial in symptomatic functional TR

Quality assessment							No of patients		Effect	Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations (including publication bias where possible)	Severe TR	Trivial TR	Relative effect (95% CI)	
Mortality (adjusted HR) – severe functional TR (graded according to American Society of Echocardiography guidelines) vs. trivial functional TR (graded according to American Society of Echocardiography guidelines) (heart failure with reduced ejection fraction and trivial-severe functional TR; mean age 68 (14) years for whole cohort – mean age for prognostic factor and referent groups was 72 and 65 years, respectively; medically managed). Follow-up median 4.02 years.										
1	Cohort study	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	745	4329	Model 1: Adjusted HR 1.35 (1.11 to 1.64)[2] Model 2: Adjusted HR 1.41 (1.25 to 1.59)[3]	MODERATE

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2]Methods: multivariable analysis, including some but not all variables pre-specified in the protocol. The following variables were included: age, sex, degree of functional TR, ejection fraction, atrial fibrillation, E/e', pulmonary hypertension, Charlson comorbidity index and MAGGIC score
[3]Methods: multivariable analysis, including some but not all variables pre-specified in the protocol. The following variables were included: age, sex, degree of functional TR, ejection fraction, atrial fibrillation, E/e', pulmonary hypertension, Charlson comorbidity index and right ventricular dysfunction degree.

Table 35: Clinical evidence profile: moderate versus trivial in symptomatic functional TR

Quality assessment	No of patients	Effect	Quality

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations (including publication bias where possible)	Moderate TR	Trivial TR	Relative effect (95% CI)	
Mortality (adjusted HR) – moderate functional TR (graded according to American Society of Echocardiography guidelines) vs. trivial functional TR (graded according to American Society of Echocardiography guidelines) (heart failure with reduced ejection fraction and trivial-severe functional TR; mean age 68 (14) years for whole cohort – mean age for prognostic factor and referent groups was 71 and 65 years, respectively; medically managed). Follow-up median 4.02 years.										
1)	Cohort study	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	2255	4329	Model 1: Adjusted HR 1.14 (1.01 to 1.29)[3] Model 2: Adjusted HR 1.17 (1.07 to 1.28)[4]	LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2]Prognostic factor indirectness - includes moderate severity tricuspid regurgitation with or without symptoms, whereas in protocol ideally aimed to look at moderate + symptomatic and moderate + asymptomatic as separate prognostic factors
[3]Methods: multivariate analysis, including some but not all variables pre-specified in the protocol. The following variables were included: age, sex, degree of functional TR, ejection fraction, atrial fibrillation, E/eâ€², pulmonary hypertension, Charlson comorbidity index and MAGGIC score
[4]Methods: multivariate analysis, including some but not all variables pre-specified in the protocol. The following variables were included: age, sex, degree of functional TR, ejection fraction, atrial fibrillation, E/eâ€², pulmonary hypertension, Charlson comorbidity index and right ventricular dysfunction degree.

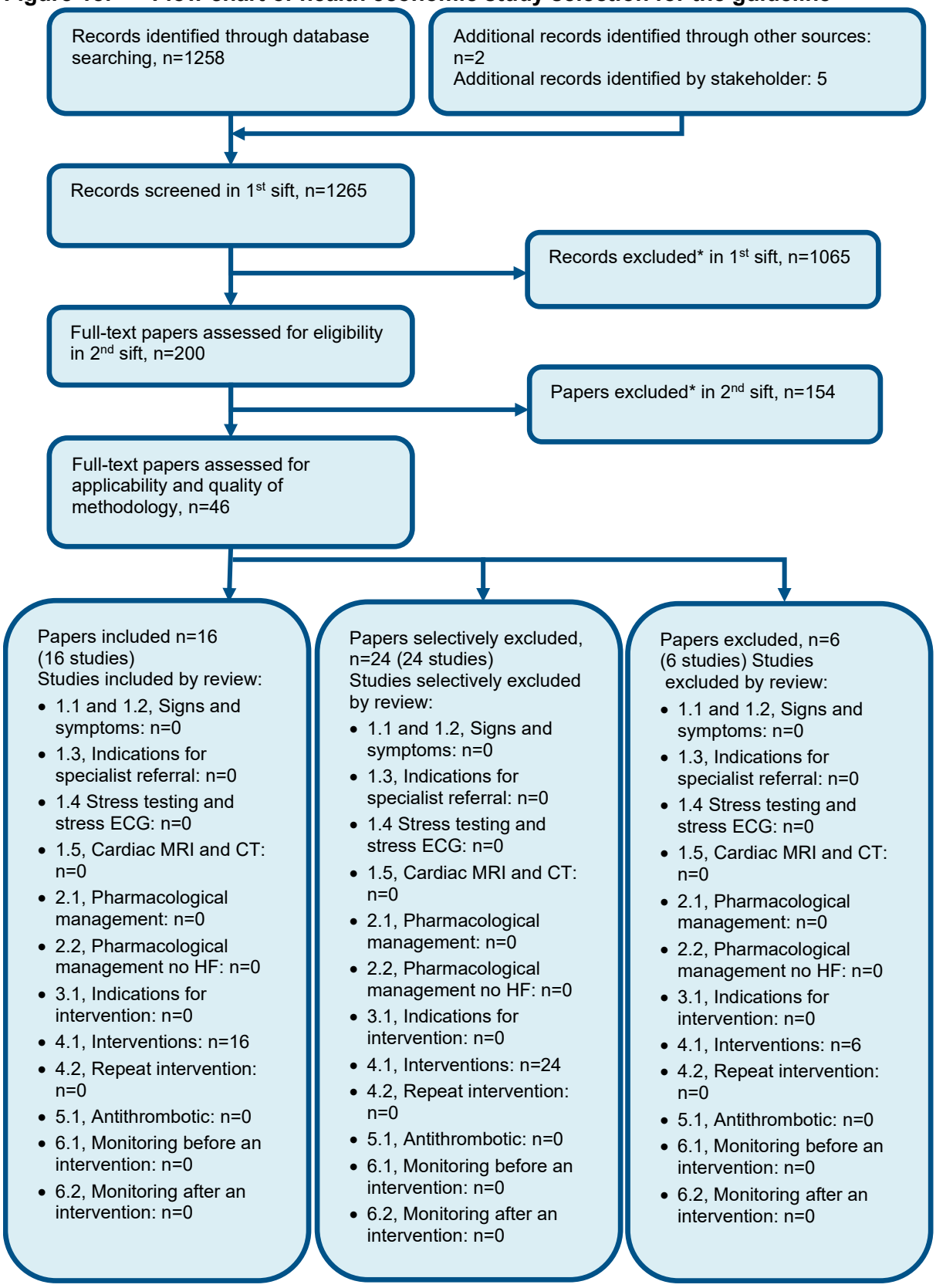
Table 36: Clinical evidence profile: severe vs. trivial, mild or moderate in functional TR with or without symptoms

Quality assessment							No of patients		Effect	Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations (including publication bias where possible)	Severe TR	Trivial-moderate TR	Relative effect (95% CI)	
All-cause mortality (adjusted HR) – severe functional TR (effective regurgitant orifice area ≥0.4 cm^2) vs. trivial, mild or moderate functional TR (effective regurgitant orifice area <0.4 cm^2) (trivial-severe functional TR due to systolic left ventricular dysfunction; mean age 70.0 (11.5) years for whole cohort – mean age for prognostic factor and referent groups was 69.3 and 70.1 years, respectively; medically managed and censored at time of surgery). Median follow-up 1.9 years.										
1	Cohort study	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	82	209	Adjusted HR 1.8 (1.16 to 2.8)[2]	LOW

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2]Methods: multivariable analysis, including some but not all variables pre-specified in the protocol. The following variables were included: effective regurgitant orifice ≥0.4 cm^2, age, sex, comorbidity index, left ventricular ejection fraction, atrial fibrillation, left atrial size, right ventricular dysfunction ≥moderate, renal failure and right ventricular systolic pressure

1 Appendix G – Economic evidence study selection

Figure 18: Flow chart of health economic study selection for the guideline



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

1

Appendix H – Economic evidence tables

None.

Appendix I – Health economic model

None.

Appendix J – Excluded studies

Clinical studies

Table 37: Studies excluded from the clinical review

Reference	Reason for exclusion
Abdel Fattah 2016[1]	Incorrect outcomes - no follow-up of patient outcomes or subsequent prognostic analysis
Alashi 2018[2]	Incorrect prognostic factors - none matching protocol
Alehagen 2005[3]	Incorrect population - not diagnosed heart valve disease
Antonini-Canterin 2018[4]	Incorrect prognostic factors - none matching protocol
Aronow 1998[5]	Incorrect population - not all with diagnosed heart valve disease; incorrect prognostic factors - none matching protocol
Avakian 2008[6]	Incorrect prognostic factors - none matching protocol
Avierinos 2002[7]	Incorrect population - not all with diagnosed heart valve disease, only 38% with mitral regurgitation in the mitral valve prolapse population.
Bach 2011[8]	Incorrect analysis - no prognostic effect sizes reported
Badran 2012[9]	Incorrect prognostic factors - none matching protocol
Baggish 2008[11]	Incorrect population - dyspnoea population and not limited to heart valve disease; incorrect prognostic factors - none matching protocol
Bahler 2018[12]	Insufficient reporting - no prognostic effect sizes reported for prognostic factors matching the protocol
Bakkestrom 2018[13]	Incorrect outcomes - no follow-up of patient outcomes or subsequent prognostic analysis
Banning 1995[14]	Incorrect analysis - no prognostic effect sizes reported
Becle 2020[15]	Incorrect prognostic factors - none matching protocol
Bergler-Klein 2004[17]	Incorrect prognostic factors - none matching protocol
Beton 1983[18]	Incorrect population - not diagnosed heart valve disease (stenosis/regurgitation), only mitral valve prolapse; incorrect analysis - no prognostic effect sizes reported
Bhattacharyya 2012[19]	Incorrect study design - narrative review.
Bohbot 2017[20]	Incorrect prognostic factors - none matching protocol
Borer 1998[21]	Insufficient reporting - no prognostic effect sizes reported, only P-values; incorrect prognostic factors - none matching protocol
Carabello 1995[22]	Incorrect study design - narrative review.
Carasso 2015[23]	Incorrect outcomes - no follow-up of patient outcomes or subsequent prognostic analysis; incorrect prognostic factors - none matching protocol
Carstensen 2016[24]	Incorrect prognostic factors - none matching protocol
Charlson 2006[25]	Incorrect prognostic factors - none matching protocol
Cheitlin 1979[27]	Incorrect analysis - no prognostic effect sizes reported
Cheitlin 2005[26]	Incorrect study design - narrative review.
Chin 2016[28]	Incorrect prognostic factors - none matching protocol; incorrect analysis - no prognostic effect sizes reported.
Chivite 2018[29]	Incorrect population - heart failure population and not all diagnosed with heart valve disease; incorrect prognostic factors - none matching protocol

Reference	Reason for exclusion
Cho 2019[30]	Insufficient controlling for confounding – univariate analysis only for factors matching the protocol and no stratification or matching
Cioffi 2016[31]	Incorrect prognostic factors - none matching protocol
Colli 2018[32]	Incorrect prognostic factors - none matching protocol
Collins 2008[33]	Incorrect study design - narrative review; incorrect population - heart failure not diagnosed heart valve disease
Coutinho 2014[34]	Incorrect prognostic factors - none matching protocol
Ducas 2020[37]	Incorrect study design - includes data from studies where all had severe disease so cannot compare between moderate/severe groups.
Dujardin 1999[38]	Incorrect prognostic factors - none matching protocol
Dupuis 2017[39]	Insufficient controlling for confounding
Enriquez-Sarano 1994[44]	Incorrect prognostic factors - none matching protocol; insufficient reporting - no prognostic effect sizes reported
Enriquez-Sarano 1994[43]	Incorrect prognostic factors - none matching protocol
Enriquez-Sarano 1995[41]	Incorrect prognostic factors - none matching protocol
Enriquez-Sarano 2015[42]	Incorrect prognostic factors - none matching protocol
Essayagh 2020[45]	Incorrect prognostic factors - none matching protocol
Essayagh 2020[46]	Incorrect population – mitral valve prolapse
Ewe 2015[47]	Incorrect prognostic factors - none matching protocol
Faggiano 1992[48]	Incorrect analysis - no prognostic effect sizes reported
Fleischmann 1997[49]	Incorrect population - not all with diagnosed heart valve disease
Fleischmann 1997[50]	Incorrect population - population with acute chest pain and not limited to those with diagnosed valve disease
Fleischmann 1997[51]	Incorrect population - population with acute chest pain and not limited to those with diagnosed valve disease; incorrect prognostic factors - none matching protocol
Frey 2019[52]	Incorrect prognostic factors - none matching protocol; incorrect analysis - no prognostic effect sizes reported
Gerdts 2015[53]	Incorrect prognostic factors - none matching protocol
Gohlke-Barwolf 2013[54]	Incorrect study design - narrative review
Guray 2004[55]	Incorrect outcomes - none matching protocol as no follow-up of patient outcomes; incorrect analysis - no prognostic effect sizes reported
Hachicha 2009[56]	Insufficient controlling for confounding
Henri 2016[57]	Incorrect prognostic factors - none matching protocol
Hering 2004[58]	Incorrect analysis - no prognostic effect sizes reported
Hochreiter 1986[59]	Incorrect analysis - no prognostic effect sizes reported
Horstkotte 1998[60]	Incorrect analysis - no prognostic effect sizes reported
Hunter 2017[61]	Incorrect population - those with chest pain not limited to HVD; incorrect study design - comparison of interventions with no apparent prognostic analysis.
Iivanainen 1996[62]	Incorrect population - not limited to those with diagnosed heart valve disease as majority of the cohort did not have any aortic stenosis at all.
Ilardi 2019[63]	Incorrect prognostic factors - none matching protocol

Reference	Reason for exclusion
Imai 2008[64]	Incorrect prognostic factors - none matching protocol; incorrect analysis - no prognostic effect sizes reported for outcomes matching the protocol
Iung 2007[65]	Incorrect prognostic factors - none matching protocol
Jansen 2015[66]	Incorrect population - not diagnosed heart valve disease; incorrect prognostic factors - none matching protocol; incorrect outcomes - none matching protocol.
Kaleschke 2011[67]	Incorrect study design - narrative review.
Kanamori 2018[68]	Incorrect prognostic factors - none matching protocol
Kang 2010[70]	Incorrect prognostic factors - none matching protocol
Kang 2012[69]	Incorrect prognostic factors - none matching protocol.
Kelly 1988[72]	Incorrect prognostic factors - none matching protocol
Kennedy 1991[73]	Insufficient reporting - no prognostic effect sizes reported for prognostic factors matching the protocol
Kim 2008[74]	Incorrect prognostic factors - none matching protocol; insufficient reporting - no prognostic effect sizes reported
Kitai 2011[75]	Incorrect prognostic factors - none matching protocol
Konety 2016[76]	Incorrect population - not limited to diagnosed heart valve disease; incorrect prognostic factors - none matching protocol
Lancellotti 2010[79]	Incorrect prognostic factors - none matching protocol
Lancellotti 2010[77]	Incorrect prognostic factors - none matching protocol
Lancellotti 2018[78]	Incorrect prognostic factors - none matching protocol
Lee 2013[80]	Incorrect prognostic factors - none matching protocol
Lee 2017[82]	Incorrect analysis - no prognostic effect sizes reported for outcomes matching the protocol
Lee 2020[81]	Incorrect prognostic factors - none matching protocol
Levy 2014[84]	Incorrect prognostic factors - none matching protocol
Levy-Neuman 2019[83]	incorrect prognostic factors - none matching protocol
Lima 2020[85]	Incorrect population – post-intervention
Lund 1990[86]	Incorrect prognostic factors - none matching protocol
Lund 1991[87]	Incorrect prognostic factors - none matching protocol
Ma 2019[88]	Incorrect analysis - no prognostic effect sizes reported for prognostic factors matching the protocol
Magne 2010[89]	Incorrect prognostic factors - none matching protocol
Magne 2012[91]	Incorrect prognostic factors - none matching protocol
Magne 2014[90]	Incorrect prognostic factors - none matching protocol
Marwick 2013[93]	Incorrect study design - health economic model comparing two different interventions
Mathieu 2017[94]	Incorrect prognostic factors - none matching protocol
Mehrotra 2018[95]	Incorrect prognostic factors - none matching protocol
Messika-Zeitoun 2004[96]	Incorrect prognostic factors - none matching protocol
Messika-Zeitoun 2004[97]	Incorrect analysis - no prognostic effect sizes reported for prognostic factors matching the protocol
Michelena 2008[98]	Incorrect prognostic factors - none matching protocol
Miura 2015[99]	Incorrect prognostic factors - none matching protocol
Miura 2019[100]	Incorrect study design - intervention rather than prognostic study, compares surgical valve replacement with medical management.

Reference	Reason for exclusion
Monin 2009[101]	Incorrect prognostic factors - none matching protocol
Murata 2019[102]	Incorrect prognostic factors - none matching protocol
Nakatsuma 2017[103]	Incorrect prognostic factors - none matching protocol
Namisaki 2019[104]	Incorrect prognostic factors - none matching protocol
Nguyen 2017[106]	Incorrect prognostic factors - none matching protocol
Nistri 2012[108]	Incorrect prognostic factors - none matching protocol
Numeroso 2014[109]	Incorrect population - those with syncope and not limited to those with diagnosed heart valve disease
Orlowska-Baranowska 2014[110]	Incorrect prognostic factors - none matching protocol as all are symptomatic severe aortic stenosis population
Otto 1997[111]	Incorrect prognostic factors - none matching protocol; insufficient reporting - no prognostic effect sizes reported, only P-values
Pellikka 2005[112]	Incorrect prognostic factors - none matching protocol
Perera 2011[114]	Incorrect analysis - no prognostic effect sizes reported; incorrect prognostic factors - none matching protocol
Pierri 2000[115]	Incorrect prognostic factors - none matching protocol
Rashedi 2014[116]	Incorrect prognostic factors - none matching protocol
Reed 1991[117]	Incorrect prognostic factors - none matching protocol
Rezzoug 2015[118]	Incorrect population - not all with diagnosed heart valve disease.
Roseman 1965[119]	Incorrect analysis - no prognostic effect sizes reported; incorrect population - initial attack was during childhood in all patients
Rosen 1994[120]	Incorrect prognostic factors - none matching protocol
Rosenhek 2006[122]	Incorrect prognostic factors - none matching protocol; incorrect analysis - no prognostic effect sizes reported
Shen 2020[123]	Incorrect study design - includes data from studies where all had severe disease so cannot compare between moderate/severe groups.
Shirai 2017[124]	Incorrect prognostic factors - none matching protocol
Siemienczuk 1989[125]	Incorrect prognostic factors - none matching protocol; incorrect analysis - no prognostic effect sizes reported
Stahle 1997[126]	Incorrect population - mitral stenosis/regurgitation and aortic stenosis/regurgitation combined rather than being stratified as in protocol, also severity is unclear
Stewart 2010[127]	Incorrect prognostic factors - none matching protocol
Sun 2019[128]	Incorrect population - not all with diagnosed heart valve disease
Supino 2007[129]	Incorrect prognostic factors - none matching protocol as all have asymptomatic severe mitral regurgitation
Suzuki 2018[130]	Incorrect population - not all with diagnosed valve disease and is in a more general echocardiography population
Taniguchi 2016[132]	Incorrect prognostic factors - none matching protocol
Taniguchi 2018[131]	Incorrect prognostic factors - none matching protocol
Tastet 2019[133]	Incorrect prognostic factors - none matching protocol
Thomassen 2017[134]	Incorrect prognostic factors - none matching protocol
Tornos 1990[136]	Incorrect analysis - no prognostic effect sizes reported; incorrect prognostic factors - none matching protocol
Tribouilloy 1999[138]	Incorrect prognostic factors - none matching protocol

Reference	Reason for exclusion
Turina 1987[139]	Incorrect analysis - no prognostic effect sizes reported
Veen 2020[140]	Incorrect prognostic factors - none matching protocol
Versekaite 2018[141]	Incorrect prognostic factors - none matching protocol
Wald 2018[142]	Incorrect prognostic factors - none matching protocol; incorrect analysis - no prognostic effect sizes reported
Wang 2011[143]	Incorrect population - general population and not focused on those with diagnosed heart valve disease; incorrect prognostic factors - none matching protocol
Yan 2017[144]	Incorrect population - general population and not focused on those with diagnosed heart valve disease; incorrect prognostic factors - none matching protocol
Zhao 2013[145]	Incorrect study design - meta-analysis of intervention studies
Zhou 2018[146]	Incorrect prognostic factors - none matching protocol

Health Economic studies

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

None.

Appendix K – Research recommendations – full details

None