National Institute for Health and Care Excellence

Final

Heart valve disease presenting in adults: investigation and management

[F] Evidence review for CT and MRI indications for intervention

NICE guideline NG208

Evidence reviews underpinning recommendations 1.3.4 to 1.3.6 and research recommendations 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 Cardiac MRI and CT in determining the need for intervention

1.1 Review question

In adults with heart valve disease, what is the prognostic value and cost effectiveness of cardiac MRI and cardiac CT to determine the need for intervention?

1.1.1 Introduction

Cardiac MRI and cardiac CT are also used in patients with heart valve disease, for assessment of the left and right ventricle, for assessment of the aorta, to identify coexistent coronary disease, and also for assessment of heart valve disease severity. Consequently, it is important to define the prognostic value and cost effectiveness of cardiac MRI and cardiac CT to determine the need for intervention.

This review aims to assess which risk factors measured on cardiac CT or cardiac MRI indicate that intervention should be performed in different valve disease presentations.

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 **requiring further tests** after echocardiography to determine whether intervention is needed. Data will be stratified by the type of heart valve disease as follows: • aortic [including bicuspid] stenosis • aortic [including bicuspid] regurgitation • mitral stenosis • mitral regurgitation • tricuspid regurgitation Exclusion: Children aged less than 18 years. Adults with congenital heart disease (excluding bicuspid aortic valves). Tricuspid stenosis and pulmonary valve disease. Adults with previous intervention for HVD (surgical or transcatheter).
Prognostic variables under consideration	**A. Cardiac MRI** **Mitral regurgitation** **Primary mitral regurgitation** • left ventricular systolic function based on ejection fraction <50% or <60% • left atrial dimensions (volume / volume index) ≥60 mL/m^2 BSA • Quantity of mitral regurgitation (regurgitant fraction [RF] or volume [RV] in ml – no accepted threshold, suggestion RF 40 or 50% and RV of 55 or 60 ml) **Secondary mitral regurgitation** • left ventricular systolic function based on ejection fraction <20%

Aortic stenosis

- left ventricular systolic function based on ejection fraction <50% or <60%
- Myocardial fibrosis (late gadolinium enhancement) (present or not in a pattern consistent with aortic stenosis, or infarction)
- Aortic valve area (<0.6cm^2/m^2 or <0.8 or 1.0 cm^2)

Aortic regurgitation

- left ventricular systolic function based on ejection fraction <50% or <60%
- Quantity of aortic regurgitation (regurgitant fraction [RF] or volume [RV] in ml – no accepted threshold, suggestion RF 30 or 40% and RV of 55 or 60 ml)
- Presence of holodiastolic flow reversal in the descending aorta

Mitral stenosis

- Valve area by direct planimetry <1.0cm^2

Tricuspid regurgitation (isolated)

- reduced right ventricular systolic function – no thresholds
- increasing right ventricular dimensions – no thresholds (dilated – mild, moderate, severe)
- Regurgitant orifice area

B. Aortic size on cardiac MRI or CT

Aortic stenosis or aortic regurgitation

- Bicuspid: aorta > 5cm or > 5.5cm
- Tricuspid: aorta > 5.5cm

C. Cardiac CT

Primary or secondary mitral regurgitation

- CT coronary angiogram: mild, moderate, or severe coronary disease of 1,2 or 3 vessels
- Severity of mitral annular calcification (mild, moderate, severe)
-

Aortic stenosis

- CT coronary angiogram: mild, moderate, or severe coronary disease of 1,2 or 3 vessels
- Aortic valve area (<0.6cm^2/m^2 or <0.8 or 1.0 cm^2)
- Calcium score of aortic valve (threshold > 2000 AU for men and >1200 AU for women)

Aortic regurgitation

- CT coronary angiogram: mild, moderate, or severe coronary disease of 1,2 or 3 vessels
-

Mitral stenosis

- CT coronary angiogram: mild, moderate, or severe coronary disease of 1,2 or 3 vessels
- Valve area by direct planimetry <1.0cm^2
- Severity of mitral valve or annular calcification (mild, moderate, severe)

	Tricuspid regurgitation CT coronary angiogram: mild, moderate, or severe coronary disease of 1,2 or 3 vessels
Confounding factors	For non-operative mortality • Age • Smoking For hospital admission for heart failure or unplanned intervention and for reduced cardiac function in those without intervention: • Age For post-operative mortality: • Age For all outcomes relating to cardiac calcium score in patients with aortic stenosis: • Age • Smoking For all other outcomes • No known confounders
Outcomes	Indication for intervention based on prognosis for the following without intervention in people under medical management: • Mortality (1 and 5 years) • Hospital admission for heart failure or unplanned intervention (1 and 5 years) • Reduced cardiac function (echo parameters – LVEF) 1 and 5 years • Symptom onset or symptom worsening (e.g. that led to surgery being required) 1 and 5 years *OR* Indication for intervention based on predictors of the following post-operative outcomes in people who have had an intervention: • Mortality (6 and 12 months) • Hospital admission for heart failure (6 and 12 months) • Reduced cardiac function (echo or cardiac MRI parameters – for example LVEF <50%) (6 and 12 months) • Return to normal LV volumes post-operatively based on echo or cardiac MRI as defined in the study (6 and 12 months) • >20% reduction in LV volume post-operatively based on echo or cardiac MRI (6 and 12 months) This may be reported as an adjusted HR, RR or OR. Sensitivity, specificity and AUC will not be included as these do not allow for multivariable adjustment. Use the time point closest to each of the listed endpoints and combine data as follows: 6 months: include 0-6 months 12 months: include >6 months up to 12 months

	1 year: include 0-12 months 5 years: include all >1 year. No minimum follow-up.
Study design	• Prospective and retrospective cohort studies that control for confounders in the study design or analysis will be included preferentially • If no controlled studies are identified, unadjusted cohort studies will be considered for inclusion. This will be assessed separately for each test and population. • Systematic reviews of the above • If no cohort studies are identified case control studies will be considered for inclusion but downgraded for risk of bias. This will be assessed separately for each test and population.

1.1.3 Methods and process

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

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 and retrospective cohort studies investigating the prognostic value of various factors measured on cardiac CT or cardiac MRI to predict outcomes in those that received conservative management of valve disease and those that received surgical treatment of valve disease. The prognostic factors were different depending on the type of valve disease (e.g. aortic regurgitation or aortic stenosis) and full details are provided in the protocol.

Twenty-seven cohort studies were included in the review;[6, 8, 9, 22, 40, 57, 62, 63, 84, 88, 94, 118, 123, 140, 152, 155, 158, 162, 187, 190, 191, 211-213, 225, 275, 291] these are summarised in Table 2 below. Evidence from these studies is summarised in Table 7-Table 11 below.

This included evidence from 22 studies for aortic stenosis, 2 studies for aortic regurgitation, 2 studies for mitral regurgitation and 1 study for functional tricuspid regurgitation.

The number of studies reporting each of the available prognostic factors within each stratum was as follows (note that some studies reported more than one prognostic factor):

- Aortic stenosis: 5/10 pre-specified risk factors
    - Cardiac MRI
        - LVEF on cardiac MRI: 3 studies[88, 123, 158]
        - myocardial fibrosis on cardiac MRI: 10 studies[6, 22, 57, 84, 88, 118, 123, 155, 187, 225]
    - Cardiac CT:
        - coronary artery disease: 3 studies[40, 152, 275]
        - aortic valve area: 1 study[62]
        - aortic valve calcium score: 9 studies[8, 9, 63, 94, 152, 162, 212, 275, 291]
- Aortic regurgitation: 1/8 pre-specified risk factors
    - Cardiac MRI

    - regurgitant fraction and regurgitant volume: 2 studies[140, 191]
- Primary mitral regurgitation: 1/5 pre-specified risk factors
  - Cardiac MRI
    - regurgitant volume: 2 studies[190, 213]
- Functional tricuspid regurgitation: 1/4 pre-specified risk factors
  - Cardiac MRI
    - right ventricular systolic function: 1 study[211]

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

- secondary mitral regurgitation
- mitral stenosis.

Note that, although studies ideally would have performed at least some form of multivariate analysis or controlled for confounders through study design, for populations and prognostic factors where there was limited or no adjusted results available, univariate results were included in the review. This was assessed individually for each population and prognostic factor combination. Studies that had not included the prespecified confounders in their multivariate analysis were still included but they were downgraded for indirectness.

Due to limited available evidence directly matching the protocol, studies that had indirect populations or prognostic factors were included but downgraded for indirectness. For example, for many studies it was unclear whether the population represented those in whom there was uncertainty about whether intervention was indicated. For some prognostic factors, studies where all participants received intervention, and therefore had an indication for intervention prior to cardiac CT or MRI results, were included due to a lack of more direct evidence.

Similarly, there were some cases where prognostic factors did not exactly match the protocol and many studies reported outcomes that were a composite of different outcomes listed separately in the protocol. In several studies, outcomes for those treated medically and those treated surgically were combined within a single analysis, rather than analysing separately as was specified in the protocol.

No pooling was possible for most outcomes due to differences in population, prognostic factor definition, which also affected the referent (comparator) group that was used in studies, or outcome reported; however, pooling of three studies was possible for the outcome of all-cause mortality following aortic valve replacement for the myocardial fibrosis on cardiac MRI prognostic factor. Although there were differences in the variables that had been adjusted for as part of the multivariate analysis, two of the three studies had included the key confounder of age in this analysis. While the other study did not account for age, this variable was very similar between the two prognostic factor groups at baseline.

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

1.1.4.2 Excluded studies

See the excluded studies list in Appendix J.

1.1.5 Summary of studies included in the prognostic evidence

Table 2: Summary of studies included in the evidence review

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
Aortic stenosis – LVEF <50% on cardiac MRI						
Everett 2020[88] N=440 UK, Germany, USA, Canada, South Korea Prospective cohort study	Severe AS scheduled for AVR: 36% in NYHA class III/IV Mean age 69.67 years	Multivariate Cox regression model	LVEF <50% on cardiac MRI	Extracellular volume percentage, age, gender, LGE on cardiac MRI and peak aortic jet velocity	All-cause mortality following aortic valve intervention – median follow-up 3.8 years	**Risk of bias**: very high **Indirectness**: • Population - all already had an indication for intervention as scheduled for aortic valve intervention
Hwang 2020[123] N=43 South Korea Prospective cohort study	Severe AS scheduled for AVR: mean NYHA class 2.1 Mean age 65.9 years	Multivariate Cox proportional hazard regression analysis	LVEF <50% on cardiac MRI	Univariate results only	Cardiovascular death, hospitalisation for cardiac causes, non-fatal stroke and symptomatic aggravation (worsening NYHA class) following AVR– median follow-up 38.8 months	**Risk of bias**: very high **Indirectness**: • Population - all already scheduled for AVR so no uncertainty as to whether there is an indication for intervention prior to cardiac MRI • Outcome - composite of multiple outcomes in the protocol
Lindsay 2016[158] N=187 UK	Those undergoing TAVI for AS: >70% with symptoms at rest or marked limitation of	Cox regression analysis	LVEF 30-49% on cardiac MRI LVEF <30% on cardiac MRI	Univariate results only	All-cause mortality following TAVI – median follow-up 850 days for whole cohort, though	**Risk of bias**: very high **Indirectness**: • Population - all already had an indication for intervention as scheduled for TAVI

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
Retrospective cohort study	physical activity and median aortic valve area on echocardiography 0.60 cm^2 in whole cohort, though unclear for those included in this analysis Median age for whole cohort was 81 years, not clear for those included in this analysis				unclear for those analysed here	• Prognostic factor - splits LVEF into two separate thresholds compared with the same referent rather than using a single threshold. Also some uncertainty as to whether measured on cardiac MRI or echocardiography, though overall details suggest this is cardiac MRI measurements
Aortic stenosis – myocardial fibrosis on cardiac MRI						
Agoston-Coldea 2019[6] N=52 Romania Prospective cohort study	Severe AS undergoing AVR: 28.8% with NYHA class ≥III Mean age 66 years	Multivariable Cox regression model	Late gadolinium enhancement (LGE) on cardiac MRI	Age, 6 minute walking distance, E/E' ratio, LVEF and LAS	Major adverse cardiac events (sudden cardiac death, non-fatal myocardial infarction, sustained ventricular arrhythmias, third-degree AV block and hospitalisation for heart failure) – median follow-up 386 days	**Risk of bias**: very high **Indirectness**: • Population - indication for intervention already present: severe AS patients undergoing AVR • Outcome - composite of multiple outcomes including some in the protocol as well as additional ones

Study	**Population**	**Analysis**	**Prognostic variables**	**Confounders**	**Outcomes**	**Limitations**
Barone-Rochette 2014[22] N=154 Belgium Prospective cohort study	Severe AS undergoing surgical AVR: 27% in NYHA class III/IV Mean age 74 years	Multivariate Cox proportional hazards model	LGE (myocardial fibrosis) on cardiac MRI	NYHA class III/IV and left bundle branch block	All-cause mortality following surgical AVR – median follow-up 2.9 years	**Risk of bias**: very high **Indirectness**: • Population - all already scheduled to have AVR so population is not those where there is uncertainty about whether or not intervention is indicated
Christensen 2017[57] N=78 Denmark Prospective cohort study	Asymptomatic severe AS Mean age 74 years for whole cohort, including some not included in fibrosis analysis	Multivariate Cox proportional hazards analysis	Fibrosis on cardiac MRI	Age, gender and aortic mean gradient	Unplanned hospital admission (for atrial fibrillation, heart failure or acute coronary syndrome), aortic valve replacement or death – median follow-up 358 days	**Risk of bias**: very high **Indirectness**: • Outcome - composite of three separate outcomes listed in the protocol
Dweck 2011[84] N=143 UK Prospective cohort study	Moderate or severe AS: symptomatic status unclear Mean age 67.2 years	Multivariate Cox proportional hazards regression	Midwall fibrosis LGE pattern on cardiac MRI Infarct fibrosis LGE pattern on cardiac MRI	LVEF, indexed LV end-diastolic volume and subsequent AVR – full list unclear but these variables are suggested based on those reported in the table	All-cause mortality (mixed medical/surgical treatment) – mean follow-up 2 years	**Risk of bias**: very high **Indirectness**: • Population - unclear whether indication for intervention was uncertain in all patients, as includes some that underwent AVR which may have been scheduled prior to cardiac MRI • Outcome - includes those with and without surgery during follow-up, whereas

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
						ideally aimed to look at results for operative and non-operative mortality separately
Everett 2020[88] N=440 UK, Germany, USA, Canada, South Korea Prospective cohort study	Severe AS scheduled for AVR: NYHA class III/IV in 36% Mean age 69.67 years	Multivariate Cox regression model	LGE on cardiac MRI	Extracellular volume percentage, age, gender, LV ejection fraction <50% and peak aortic jet velocity	All-cause mortality following AVR – median follow-up 3.8 years	**Risk of bias**: very high **Indirectness**: • Population – all already scheduled for aortic valve intervention so no uncertainty about whether there is indication for intervention.
Herrmann 2018[118] N=46 Germany Prospective cohort study	Symptomatic severe AS referred for AVR Mean age 68.3 years	Multivariate Cox proportional hazards regression	Mild fibrosis on cardiac MRI Severe fibrosis on cardiac MRI	Varied depending on model Model 1: age and sex Model 2: EuroSCORE	All-cause mortality – follow-up was 10 years 9 months in 57/58 enrolled patients (46 had data for fibrosis and unclear whether the one patient that was lost to follow-up was part of this analysis)	**Risk of bias**: very high **Indirectness**: • Population - all were symptomatic severe AS undergoing AVR, so already have an indication for intervention prior to cardiac MRI • Prognostic factor - specific severity of fibrosis on cardiac MRI compared with no fibrosis rather than comparing any fibrosis with no fibrosis
Hwang 2020[123] N=43 South Korea Prospective cohort study	Severe AS scheduled for AVR: mean NYHA class 2.1 Mean age 65.9 years	Multivariate Cox proportional hazard regression analysis	Diffuse myocardial fibrosis on cardiac MRI	Atrial fibrillation, anaemia and mild renal dysfunction	Cardiovascular death, hospitalisation for cardiac causes, non-fatal stroke and symptomatic aggravation	**Risk of bias**: very high **Indirectness**: • Population - all already scheduled for AVR so no uncertainty as to whether there is an indication for

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
					(worsening NYHA class) following AVR– median follow-up 38.8 months	intervention prior to cardiac MRI • Outcome - composite of multiple outcomes in the protocol
Lee 2018[155] N=127 South Korea Prospective cohort study	Moderate or severe AS: proportion with severe AS was 62.2% and with any typical AS symptoms was 54.5% Mean age 68.8 years 69% had AVR during follow-up	Multivariate Cox regression analysis	LGE on cardiac MRI	EuroSCORE II, prior use of diuretics and being within highest native T1 value tertile	All-cause mortality and unexpected hospitalisation for heart failure during follow-up (mixed medical and surgical treatment)	**Risk of bias**: very high **Indirectness**: • Population - includes a large proportion that were already deemed to have an indication for intervention regardless of cardiac MRI • Outcome - composite outcome of multiple outcomes in protocol. Also includes those with and without operation in the analysis, whereas ideally aimed to analyse operative and non-operative outcomes separately.
Musa 2018[187] N=613 UK Prospective cohort study	Severe AS undergoing AVR: proportion with NYHA class ≥III was 40.1% Median age 74.6 years	Multivariate Cox proportional hazards model	LGE on cardiac MRI (LV myocardial scar)	Varied depending on the outcome All-cause mortality post-intervention: RV ejection fraction on cardiac MRI, LVEF on cardiac MRI, indexed atrial volume on cardiac MRI, atrial fibrillation, LV maximal wall thickness, STS score, LV stroke volume score on cardiac MRI,	All-cause mortality post-intervention Cardiovascular mortality post-intervention Median follow-up was 3.6 years	**Risk of bias**: very high **Indirectness**: • Population - all already scheduled for AVR so does no uncertainty about whether intervention is indicated

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
				coronary artery disease, aortic valve area on echocardiography and age Cardiovascular mortality post-intervention: gender, previous coronary artery disease, LVEF on cardiac MRI, atrial fibrillation and age		
Rajesh 2017[225] N=109 India Prospective cohort study	Severe AS with/without symptom: 16.5% were in NYHA class III/IV Mean age 57.3 years 34.9% had AVR	Multivariate logistic regression analysis	LGE on cardiac MRI	Age >62 years, NYHA class III/IV, current smoker, modified Simpsons LVEF, LV mass on cardiac MRI, peak velocity and valvuloarterial impedance	Mortality, LVEF drop ≥20%, new-onset heart failure or hospitalisation for cardiovascular causes and new-onset arrythmia (mixed medical/surgical treatment – mean follow-up 13 months	**Risk of bias**: very high **Indirectness**: • Population - 35% already deemed to have indications for intervention regardless of cardiac MRI results • Outcome - composite of multiple factors listed in protocol, as well as some not listed in protocol. Also includes medically managed and surgically managed patients in the same analysis, whereas ideally aimed to analyse postoperative and non-operative outcomes separately.
Aortic stenosis – coronary artery disease on CT						
Carstensen 2016[40] N=104 Denmark	Asymptomatic moderate-severe AS	Cox regression analysis	Significant stenosis (>50% luminal diameter) of 1, 2 or 3 vessels on CT	No multivariable analysis, unadjusted RR calculated from	Indication for AVR during follow-up –	**Risk of bias**: very high **Indirectness**: • None identified

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
Prospective cohort study	Mean age 72 years		OR Significant stenosis (>50% luminal diameter) of 1, 2 or 3 vessels or atheromatosis on CT	number of events reported in each group	median follow-up 2.3 years	Note: Cohort overlaps with Larsen 2016[152]
Larsen 2016[152] N=116 Denmark Prospective cohort study	Asymptomatic mild-severe AS: mean aortic valve area on echocardiography was 1.01 cm^2 Mean age 72 years	Cox proportional hazards regression model	Coronary artery disease >70% stenosis on CT	Univariate results only	Indication for AVR during follow-up – median follow-up 27 months	**Risk of bias**: very high **Indirectness**: • None identified Cohort overlaps with Carstensen 2016[40]
Utsunomiya 2013[275] N=64 Japan Prospective cohort study	Asymptomatic mild-severe AS: 45% being severe cases Mean age 74 years	Cox regression analysis	Multivessel obstructive coronary artery disease on CT	Age, gender, baseline systolic and diastolic blood pressure, peak transaortic velocity ≥4 m/s, aortic valve area on CCTA, LVEF on CCTA, LV mass index on CCTA and aortic valve calcium score	Cardiac events (cardiac death, AVR, non-fatal myocardial infarction and heart failure requiring urgent hospitalisation) – median follow-up 29 months	**Risk of bias**: very high **Indirectness**: • Population - unclear whether there is uncertainty regarding indication for intervention in all patents, as includes mild-severe asymptomatic AS patients, with only 45% being asymptomatic severe • Outcome - composite of multiple outcomes specified in the protocol.
Aortic stenosis – aortic valve area on CT						

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
Clavel 2015[62] N=269 France Prospective cohort study	AS patients undergoing CT and echocardiography in same episode of care: 45% with NYHA class III/IV and mean aortic valve area 0.94 cm^2 Mean age 76 years	Multivariable Cox proportional hazards regression model	Aortic valve area ≤1.2 cm^2 on CT Aortic valve area ≤1.0 cm^2 on CT	Age-adjusted Charlson score index, sex, symptoms, mean gradient and LVEF	Mortality under medical management – mean follow-up 3.2 years	**Risk of bias**: high **Indirectness**: • None identified
Aortic stenosis – aortic valve calcium score on CT						
Akodad 2018[8] N=118 France Prospective cohort study	Those undergoing TAVI for AS: >50% NYHA class ≥3 and mean gradient consistent with severe AS. Mean age 83.2 years	Multivariate logistic regression	Calcium score >6,000 HU on CT	Adjusted but list of variables included unclear	All-cause mortality, stroke, myocardial infarction, heart failure or rehospitalisation for cardiac causes - 1 month post-TAVI Rehospitalisation (unclear if all or only cardiac causes) - 1 month post-TAVI	**Risk of bias:** very high **Indirectness**: • Population - all had TAVI so already an indication for intervention • Prognostic factor - threshold of 6,000 HU used different to suggested thresholds in protocol and same one used for men and women • Outcome - composite of multiple outcomes in protocol as well as some not listed in protocol
Aksoy 2014[9] N=21 included in analysis that underwent AVR	Low-flow low-gradient severe AS undergoing surgical aortic valve	Cox proportional hazards analysis	Calcium score >2027 on CT	No multivariable analysis within this subgroup, unadjusted estimate of HR	Mortality post-AVR – 30 days post-AVR	**Risk of bias**: very high **Indirectness**: • Prognostic factor - same threshold used for men

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
USA Retrospective cohort study	replacement (AVR) Mean age and further details for the subgroup undergoing surgical AVR unclear			calculated using data provided in the paper		and women rather than a separate one as in protocol
Clavel 2014[63] N=794 USA, France, Canada Prospective cohort study	At least mild AS under conservative management: 27% with heart failure symptoms and mean gradient 35 mmHg Mean age 73 years	Multivariate Cox proportional hazards model	Severe aortic valve calcification (≥2065 in AU in men and ≥1274 AU in women) on CT	Age, sex, NYHA class ≥III, diabetes, history of coronary artery disease, indexed aortic valve area, mean gradient and LVEF	Mortality under conservative management – mean follow-up 1.7 years	**Risk of bias**: very high **Indirectness**: • Population - unclear if there was uncertainty about whether to intervene as includes mild-severe AS under conservative management
Fischer-Rasokat, 2020[94] N=650 Germany Retrospective cohort study	Severe AS in as TAVI registry. Categorised as low-flow, low-gradient (LFLG), paradoxical LFLG, normal-flow, low-gradient	Multivariate Cox proportional hazards model	Aortic valve calcium score (low/high) on CT Threshold ≥1200 AU in women and ≥2000 AU in men.	BMI, GFR, dyslipidaemia, LV hypertrophy, mean pressure gradient, aortic valve area index, balloon expandable valve, rapid pacing, residual AR.	All-cause mortality at 1 year after TAVI	**Risk of bias**: very high **Indirectness**: • Population - all had TAVI so already an indication for intervention
Larsen 2016[152] N=115 Denmark	Asymptomatic mild-severe AS: mean aortic valve area on echocardiography was 1.01 cm^2	Cox proportional hazards regression	Severe aortic valve calcium density (>300 AU/cm^2 for women and >475 AU/cm^2 for men) on CT	Only univariate results available	Indication for AVR during follow-up – median follow-up 27 months	**Risk of bias**: very high **Indirectness**: • Prognostic factor – calcium density relative to area

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
Prospective cohort study	Mean age 72 years					rather than calcium score of the valve.
Ludwig 2020[162] N=526 Germany Retrospective cohort study	Severe low LVEF low-flow, low-gradient (LFLG) and paradoxical LFLG AS undergoing TAVI Median age 79.9 years in LFLG and 82.2 in pLFLG subgroups	Multivariate Cox proportional hazards model	Aortic valve calcium density on CT (based on total calcium in the annular plane and the LVOT: high, medium, low	Age, BMI, diabetes, COPD, atrial fibrillation, prior myocardial infarction (for pLFLG only), non-TF access.	Mortality up to 3 years after TAVI	**Risk of bias**: high **Indirectness**: • Population - all had TAVI so already an indication for intervention • Prognostic factor – calcium density relative to area rather than calcium score of the valve.
Pawade 2018[212] N=215 UK, Canada, France, Spain, USA Multicentre registry with primarily prospective data	Various AS presentations, including mild-severe with symptom status varying between patients (only includes those where decision on whether to perform an intervention had not been made prior to CT in outcome analysis) Mean age 77 years	Cox proportional hazards regression	Severe aortic valve calcium (≥1274 AU for women and ≥2065 AU for men) on CT	Age, sex, Vmax ≥4 m/s and aortic valve area <1.0 cm^2	Death or AVR during follow-up – median follow-up 1029 days	**Risk of bias**: very high **Indirectness**: • Outcome - composite of two separate outcomes listed in the protocol. Also unclear whether AVR captures only unplanned intervention as in our protocol, or whether some were planned procedures following CT results.

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
Utsunomiya 2013[275] N=64 whole cohort (n=29 in asymptomatic severe subgroup) Japan Prospective cohort study	<u>Whole cohort:</u> Asymptomatic mild-severe AS (45% being severe cases) Mean age 74 years <u>Asymptomatic severe subgroup:</u> Mean age and other details for this subgroup not reported	Cox regression analysis	Aortic valve calcium score ≥723 on CT – whole cohort Aortic valve calcium score ≥1266 – asymptomatic severe subgroup	No multivariable analysis, unadjusted estimates of HR calculated using KM curves and number at risk or other details reported in the paper	Cardiac events (cardiac death, AVR, non-fatal myocardial infarction and heart failure requiring urgent hospitalisation) Non-AVR cardiac events (cardiac death, non-fatal myocardial infarction and heart failure requiring urgent hospitalisation) Median follow-up for whole cohort was 29 months, but was not clear for the asymptomatic severe subgroup	**Risk of bias**: very high **Indirectness**: <u>Whole cohort</u> • Population - unclear if there is uncertainty about whether to intervene, as includes mixture of mild-severe asymptomatic AS with only 45% severe • Prognostic factor - threshold is quite different to that specified in the protocol and the same one has been used for men and women, rather than using a separate threshold • Outcome - composite of multiple outcomes listed in the protocol <u>Asymptomatic severe subgroup:</u> • Prognostic factor - threshold is the same one has been used for men and women, rather than using a separate threshold • Outcome - composite of multiple outcomes listed in the protocol
Yoon 2020[291] N=1034	<u>Bicuspid aortic valve undergoing TAVI for</u>	Multivariate Cox proportional hazards model	Excess leaflet calcification on CT (more than the median value for	Age, STS score, peripheral vascular disease, prior AF, calcified raphe,	All-cause mortality after TAVI	**Risk of bias**: high for all-cause mortality, very high for cardiovascular mortality

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
Denmark, France, Germany, Israel, Italy, the Netherlands, Switzerland, and USA Mixed prospective/retrospective cohort study	symptomatic severe AS Mean age 74.7 (9.3)		the cohort, >382 mm^3)	aortopathy, non-TF access.	Median follow-up 360 days Cardiovascular mortality	**Indirectness**: • Population - all had TAVI so already an indication for intervention • Prognostic factor – calcium density relative to area rather than calcium score of the valve.
Aortic regurgitation – regurgitant fraction and regurgitant volume on cardiac MRI						
Kockova 2019[140] N=104 Czech Republic Prospective cohort study	Asymptomatic moderate-severe or severe aortic regurgitation Mean age 44 years	Multivariable Cox proportional hazards regression model	Aortic regurgitant fraction <34% on cardiac MRI Aortic regurgitant volume <45 ml on cardiac MRI	MRI-derived LV volumes or their indices	Aortic valve surgery during follow-up – median follow-up 587 days	**Risk of bias**: very high **Indirectness**: • None identified
Myerson 2012[191] N=113 UK Retrospective cohort study	Asymptomatic moderate or severe chronic aortic regurgitation Mean age 49 years	Multivariable Cox proportional hazards regression model	AR fraction ≤33% on cardiac MRI AR volume ≤42 ml on cardiac MRI	Appears to be adjusted for regurgitant volume and LV end-diastolic volume, though this is unclear	Development of an indication for surgery during follow-up – mean follow-up 2.6 years	**Risk of bias**: very high **Indirectness**: • None identified
Mitral regurgitation – regurgitant volume on cardiac MRI						

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
Myerson 2016[190] N=109 UK Prospective cohort study	Asymptomatic moderate or severe chronic organic mitral regurgitation Mean age 64.8 years	Cox proportional hazards regression model	Mitral regurgitant volume ≤55 ml on cardiac MRI	Univariate results only	Indication for surgery during follow-up – mean follow-up 2.5 years	**Risk of bias**: very high **Indirectness**: • None identified
Penicka 2018[213] N=258 Belgium and Czech Republic Prospective cohort study	Asymptomatic, chronic moderate and severe organic MR attributable to flail or prolapse	Cox proportional hazards regression model	Mitral regurgitant volume per 10 mL on cardiac MRI	Age, sex, and LVESVI on MRI.	All-cause mortality Indication for mitral valve surgery – median follow-up 5.0 (IQR 3.5-6.0) years	**Risk of bias**: very high **Indirectness**: None identified
Tricuspid regurgitation – right ventricular function on cardiac MRI						
Park 2016[211] N=75 South Korea Prospective cohort study	Severe isolated functional tricuspid regurgitation (TR) undergoing TR surgery: 54.7% in NYHA class III/IV Mean age 59.3 years	Multivariate/univariate Cox proportional hazards model (depending on prognostic factor)	Right ventricular ejection fraction (RVEF) per 5% higher (continuous) RVEF <46% on cardiac MRI Right ventricular end systolic volume index (RV-ESVI) per 10 ml/m^2 increase (continuous)	Continuous variable analyses for RVEF and RV-ESVI are adjusted for age, sex, NYHA class, haemoglobin level and glomerular filtration rate Results for other prognostic factors are unadjusted	Cardiac death following TR surgery – median follow-up 57 months	**Risk of bias**: very high **Indirectness**: • Population - all underwent intervention for severe functional TR so does not represent population where there is uncertainty about whether there is an indication for intervention • Outcome - only includes cardiac deaths and not all deaths.

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
			RV-ESVI ≥76 ml/m^2 All on cardiac MRI			

See Appendix D for full evidence tables.

1.1.6 Summary of the prognostic evidence

Aortic stenosis

Table 3: Clinical evidence summary: LVEF on cardiac MRI

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Risk of bias	Imprecision	Indirectness	GRADE Quality
LVEF **<50% vs ≥50%** on cardiac MRI for predicting **all-cause mortality following aortic valve intervention** – median follow-up 3.8 years (severe AS scheduled for AVR, 36% in NYHA class III/IV; mean age 69.67 years)	1 (n=440)	Adjusted HR: 1.53 (0.76 to 3.06)[a]	Very serious[b]	Serious[c]	Serious[d]	VERY LOW
LVEF **<50% vs ≥50%** on cardiac MRI for predicting **cardiovascular death, hospitalisation for cardiac causes, non-fatal stroke and symptomatic aggravation** (worsening NYHA class) **following AVR**– median follow-up 38.8 months (severe AS scheduled for AVR, mean NYHA class 2.1; mean age 65.9 years)	1 (n=43)	Unadjusted HR: 1.598 (0.567 to 4.505)[e]	Very serious[b]	Serious[c]	Very serious[f]	VERY LOW
LVEF **30-49% vs ≥50%** on cardiac MRI for predicting **all-cause mortality following TAVI** – median follow-up 850 days for whole cohort, though unclear for those analysed here (those undergoing TAVI for AS, >70% with symptoms at rest or marked limitation of physical activity and median aortic valve area on echocardiography 0.60 cm^2 in whole cohort, though unclear for those included in this analysis; median age for whole cohort was 81 years, not clear for those included in this analysis)	1 (n=173)	Unadjusted HR: 1.19 (0.69 to 2.04)[e]	Very serious[b]	Serious[c]	Very serious[g]	VERY LOW
LVEF **<30% vs ≥50%** on cardiac MRI for predicting **all-cause mortality following TAVI** – median follow-up 850 days for whole cohort, though unclear for those analysed here	1 (n=122)	Unadjusted HR: 2.54 (1.17 to 5.53)[e]	Very serious[b]	None	Very serious[g]	VERY LOW

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Risk of bias	Imprecision	Indirectness	GRADE Quality
(those undergoing TAVI for AS, >70% with symptoms at rest or marked limitation of physical activity and median aortic valve area on echocardiography 0.60 cm^2 in whole cohort, though unclear for those included in this analysis; median age for whole cohort was 81 years, not clear for those included in this analysis)						

(a) Methods: multivariable analysis, adjusted for extracellular volume percentage, age, gender, LGE on cardiac MRI and peak aortic jet velocity (age prespecified in protocol was adjusted for)

(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 null line

(d) Population - all already have an indication for intervention as scheduled for aortic valve intervention

(e) Methods: no multivariable analysis, unadjusted HR reported in the paper

(f) Population - all already scheduled for AVR so no uncertainty as to whether there is an indication for intervention prior to cardiac MRI; and outcome - composite of multiple outcomes in the protocol combined rather than reported separately

(g) Population - all already have an indication for intervention as scheduled for TAVI; and prognostic factor - splits LVEF into two separate thresholds compared with the same referent rather than using a single threshold. Also some uncertainty as to whether measured on cardiac MRI or echocardiography, though overall details suggest this is cardiac MRI measurements

Table 4: Clinical evidence summary: Myocardial fibrosis on cardiac MRI

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Risk of bias	Imprecision	Indirectness	GRADE Quality
Mortality outcomes						
Midwall fibrosis LGE pattern compared to no LGE on cardiac MRI for predicting **all-cause mortality** (mixed medical/surgical treatment) – mean follow-up 2 years (moderate or severe AS, symptomatic status unclear; mean age 67.2 years)	1 (n=103)	Adjusted HR: 5.35 (1.17 to 24.56)[a]	Very serious[b]	None	Very serious[c]	VERY LOW
Infarct fibrosis LGE pattern compared to no LGE on cardiac MRI for predicting **all-cause mortality** (mixed medical/surgical treatment) – mean follow-up 2 years	1 (n=89)	Adjusted HR: 2.56 (0.48 to 13.65)[a]	Very serious[b]	serious[d]	Very serious[c]	VERY LOW

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Risk of bias	Imprecision	Indirectness	GRADE Quality
(moderate or severe AS, symptomatic status unclear; mean age 66.7 years)						
Mild fibrosis compared to no fibrosis on cardiac MRI for predicting **all-cause mortality** – follow-up was 10 years 9 months in 57/58 enrolled patients (46 had data for fibrosis and unclear whether the one patient that was lost to follow-up was part of this analysis) (symptomatic severe AS referred for AVR; mean age 68.3 years)	1 (n not reported)	Adjusted HR: • Model 1: 2.52 (0.60 to 10.66)[e] • Model 2: 2.98 (0.74 to 11.96)[f]	Very serious[b]	Serious[d]	Very serious[g]	VERY LOW
Severe fibrosis compared to no fibrosis on cardiac MRI for predicting **all-cause mortality** – follow-up was 10 years 9 months in 57/58 enrolled patients (46 had data for fibrosis and unclear whether the one patient that was lost to follow-up was part of this analysis) (symptomatic severe AS referred for AVR; mean age 68.3 years)	1 (n not reported)	Adjusted HR: • Model 1: 6.03 (1.66 to 21.91)[e] • Model 2: 3.70 (0.93 to 14.72)[f]	Very serious[b]	None for model 1 Serious[d] for model 2	Very serious[g]	VERY LOW
Composite outcomes						
LGE compared to no LGE on cardiac MRI for predicting **all-cause mortality and unexpected hospitalisation for heart failure** during follow-up (mixed medical and surgical treatment) – median follow-up 27.9 months (moderate or severe AS, proportion with severe AS was 62.2% and with any typical AS symptoms was 54.5%; mean age 68.8 years; 69% had AVR during follow-up)	1 (n=127)	Adjusted HR: 1.56 (1.05 to 2.32)[h]	Very serious[b]	None	Very serious[i]	VERY LOW
Fibrosis compared to no fibrosis on cardiac MRI for predicting **unplanned hospital admission** (for atrial fibrillation, heart failure or acute coronary syndrome), **aortic valve replacement or death** – median follow-up 358 days (asymptomatic severe AS; mean age 74 years for whole cohort, including some not included in fibrosis analysis)	1 (n=78)	Adjusted HR: 1.17 (0.44 to 3.11)[j]	Very serious[b]	Serious[d]	Serious[k]	VERY LOW

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Risk of bias	Imprecision	Indirectness	GRADE Quality
LGE compared to no LGE on cardiac MRI for predicting **mortality, LVEF drop ≥20%, new-onset heart failure or hospitalisation for cardiovascular causes and new-onset arrythmia** (mixed medical/surgical treatment) – mean follow-up 13 months (severe AS with/without symptoms, 16.5% were in NYHA class III/IV and unclear proportion in NYHA class II; mean age 57.3 years; 34.9% had AVR)	1 (n=109)	Adjusted OR: 1.68 (0.61 to 4.60)[l]	Very serious[b]	Serious[d]	Very serious[m]	VERY LOW
LGE (myocardial fibrosis) compared to no LGE on cardiac MRI for predicting **major adverse cardiac events** (sudden cardiac death, non-fatal myocardial infarction, sustained ventricular arrhythmias, third-degree AV block and hospitalisation for heart failure) – median follow-up 386 days (severe AS undergoing AVR, 28.8% with NYHA class ≥III; mean age 66 years)	1 (n=52)	Adjusted HR: 11.30 (1.82 to 70.18)[n]	Serious[b]	None	Very serious[o]	VERY LOW
Post-intervention outcomes in severe AS						
LGE (myocardial fibrosis) compared to no LGE on cardiac MRI for predicting **all-cause mortality post-intervention** – median follow-up was 2.9-3.8 years across the studies (severe AS undergoing AVR, proportion with NYHA class ≥III differed between studies but was similar (36%, 40.1% and 27%), age was similar across studies (mean, 69.67 years; mean, 74 years; and median, 74.6 years)	3 (n=1207)	Adjusted HR: 1.94 (1.34 to 2.80)[p]	Very serious[b]	None	Serious[q]	VERY LOW
LGE (myocardial fibrosis) compared to no LGE on cardiac MRI for predicting **cardiovascular mortality post-intervention** – median follow-up was 3.6 years (severe AS undergoing AVR, proportion with NYHA class ≥III was 40.1%; median age 74.6 years)	1 (n=613)	Adjusted HR: 3.14 (1.65 to 5.98)[r]	Serious[b]	None	Serious[q]	LOW

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Risk of bias	Imprecision	Indirectness	GRADE Quality
Diffuse myocardial fibrosis compared to normal myocardium on cardiac MRI for predicting **cardiovascular death, hospitalisation for cardiac causes, non-fatal stroke and symptomatic aggravation** (worsening NYHA class) **following AVR**– median follow-up 38.8 months (severe AS scheduled for AVR, mean NYHA class 2.1; mean age 65.9 years)	1 (n=43)	Adjusted HR: 5.52 (1.03 to 29.51)[s]	Very serious[b]	None	Very serious[t]	VERY LOW

(a) Methods: multivariable analysis, adjusted for LVEF, indexed LV end-diastolic volume and subsequent AVR – full list unclear but these variables are suggested based on those reported in the table (does not include age or smoking, which were prespecified in the protocol)

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

(c) Population - unclear whether indication for intervention was unclear in all patients, as includes some that underwent AVR which may have been scheduled prior to cardiac MRI; prognostic factor - provides results separately for two types of LGE on cardiac MRI rather than as a single combined result vs. no LGE on cardiac MRI; and outcome - includes those with and without surgery during follow-up, whereas ideally aimed to look at results for operative and non-operative mortality separately

(d) 95% CI crosses null line

(e) Methods: multivariable analysis, adjusted for age and sex (includes the prespecified confounder of age)

(f) Methods: multivariable analysis, adjusted for EuroSCORE (includes the prespecified confounder of age as age is a component of the EuroSCORE)

(g) Population - all were symptomatic severe AS undergoing AVR, so already have an indication for intervention prior to cardiac MRI; and prognostic factor - specific severity of fibrosis on cardiac MRI compared with no fibrosis rather than comparing any fibrosis with no fibrosis

(h) Methods: multivariable analysis, adjusted for EuroSCORE II, prior use of diuretics and being within highest native T1 value tertile (does not include age or smoking which were prespecified in the protocol, though age is one of the components of EuroSCORE II which has been included)

(i) Population - includes a large proportion that were already deemed to have an indication for intervention regardless of cardiac MRI results; and outcome - composite outcome of multiple outcomes in protocol combined rather than reported separately. Also includes those with and without operation in the analysis, whereas ideally aimed to analyse operative and non-operative outcomes separately.

(j) Methods: multivariable analysis, adjusted for age, gender and aortic mean gradient (includes age prespecified in the protocol but not smoking)

(k) Outcome - composite of three separate outcomes listed in the protocol rather than reporting them separately

(l) Methods: multivariable analysis, adjusted for age >62 years, NYHA class III/IV, current smoker, modified Simspons LVEF, LV mass on cardiac MRI, peak velocity and valvuloarterial impedance (includes age and smoking which were prespecified in the protocol)

(m) Population - 35% already deemed to have indications for intervention regardless of cardiac MRI results; and outcome - composite of multiple factors listed in protocol, as well as some not listed in protocol, rather than reporting separately. Also includes medically managed and surgically managed patients in the same analysis, whereas ideally aimed to analyse postoperative and non-operative outcomes separately.

(n) Methods: multivariable analysis, adjusted for age, 6 minute walking distance, E/E’ ratio, LVEF and LAS (includes age prespecified in the protocol)

(o) Population - indication for intervention already present as population was severe AS patients undergoing AVR; and outcome - composite of multiple outcomes including some of those in protocol as well as additional ones

(p) Methods: multivariable analysis, variables included differed between studies. The prespecified confounder of age was adjusted for in two of the studies and age was similar between LGE and no LGE groups for the third study. One study adjusted for NYHA class III/IV and left bundle branch block, one study adjusted for extracellular volume percentage, age, gender, LVEF

<50% and peak aortic jet velocity and one study adjusted for RV ejection fraction on cardiac MRI, LVEF on cardiac MRI, indexed atrial volume on cardiac MRI, atrial fibrillation, LV maximal wall thickness, STS score, LV stroke volume score on cardiac MRI, coronary artery disease, aortic valve area on echocardiography and age

(q) *Population - all already scheduled for AVR so does not represent population where there is uncertainty about whether or not intervention is indicated*

(r) *Methods: multivariable analysis, adjusted for gender, previous coronary artery disease, LVEF on cardiac MRI, atrial fibrillation and age (prespecified confounder of age was included)*

(s) *Methods: multivariable analysis, adjusted for atrial fibrillation, anaemia and mild renal dysfunction (does not include age which was prespecified in the protocol)*

(t) *Population - all already scheduled for AVR so no uncertainty as to whether there is an indication for intervention prior to cardiac MRI; and outcome - composite of multiple outcomes in the protocol combined rather than reported separately*

Table 5: Clinical evidence summary: coronary artery disease on CT

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Risk of bias	Imprecision	Indirectness	GRADE Quality
Significant stenosis (>50% luminal diameter) of 1, 2 or 3 vessels or atheromatosis compared to normal coronary angiogram on CT for predicting **indication for AVR** during follow-up Median follow-up 2.3 years (unadjusted RR calculated from number of events reported in each group) (asymptomatic moderate-severe AS; mean age 72 years)	1 (n=104)	Unadjusted RR: 1.15 (0.61 to 2.18)[a]	Very serious[b]	Serious[c]	None	VERY LOW
Significant stenosis (>50% luminal diameter) of 1, 2 or 3 vessels compared to normal coronary angiogram or atheromatosis on CT for predicting **indication for AVR** during follow-up median follow-up 2.3 years (unadjusted RR calculated from number of events reported in each group) (asymptomatic moderate-severe AS; mean age 72 years)	1 (n=104)	Unadjusted RR: 1.33 (0.84 to 2.11)[a]	Very serious[b]	Serious[c]	None	VERY LOW
Coronary artery disease >70% stenosis compared to ≤70% stenosis on CT for predicting **indication for AVR** during follow-up – median follow-up 27 months	1 (n=116)	Unadjusted HR: 1.79 (0.93 to 3.44)[d]	Very serious[b]	Serious[c]	None	VERY LOW

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Risk of bias	Imprecision	Indirectness	GRADE Quality
(asymptomatic mild-severe AS, mean aortic valve area on echocardiography was 1.01 cm^2; mean age 72 years)						
Multivessel obstructive coronary artery disease compared to no multivessel coronary artery disease on CT for predicting **cardiac events** (cardiac death, AVR, non-fatal myocardial infarction and heart failure requiring urgent hospitalisation) Median follow-up 29 months (asymptomatic mild-severe AS, with 45% being severe cases; mean age 74 years)	1 (n=64)	Adjusted HR: 2.70 (0.95 to 7.65)[e]	Very serious[b]	Serious[c]	Very serious[f]	VERY LOW

(a) Methods: no multivariable analysis, unadjusted RR calculated from number of events reported in each group

(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 null line

(d) Methods: no multivariable analysis, univariate HR reported in the paper

(e) Methods: multivariable analysis, adjusted for age, gender, baseline systolic and diastolic blood pressure, peak tranaortic velocity ≥4 m/s, aortic valve area on CCTA, LVEF on CCTA, LV mass index on CCTA and aortic valve calcium score (age prespecified in protocol was adjusted for but smoking was not)

(f) Population - unclear whether there is uncertainty regarding indication for intervention in all patents, as includes mild-severe asymptomatic AS patients, with only 45% being asymptomatic severe; and outcome - composite of multiple outcomes specified in the protocol rather than being reported separately

Table 6: Clinical evidence summary: Aortic valve area on CT

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Risk of bias	Imprecision	Indirectness	GRADE Quality
Aortic valve area **≤1.2 cm^2 compared to >1.2 cm^2** on CT for predicting **mortality under medical management** Mean follow-up 3.2 years (AS patients undergoing CT and echocardiography in same episode of care, 45% with NYHA class III/IV, mean aortic valve area 0.94 cm^2; mean age 76 years)	1 (n=269)	Adjusted HR: 3.16 (1.60 to 6.26)[a]	Serious[b]	None	None	MODERATE

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Risk of bias	Imprecision	Indirectness	GRADE Quality
Aortic valve area **≤1.0 cm^2 compared to >1.0 cm^2** on CT for predicting **mortality under medical management** Mean follow-up 3.2 years (AS patients undergoing CT and echocardiography in same episode of care, 45% with NYHA class III/IV, mean aortic valve area 0.94 cm^2; mean age 76 years)	1 (n=269)	Adjusted HR: 1.43 (0.77 to 2.64)[a]	Serious[b]	Serious[c]	None	LOW

(a) Methods: multivariable analysis, adjusted for age-adjusted Charlson score index, sex, symptoms, mean gradient and LVEF (age prespecified in protocol was adjusted for but smoking was not)

(a) 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

(b) 95% CI crosses null line

Table 7: Clinical evidence summary: aortic valve calcium score on cardiac CT

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Risk of bias	Imprecision	Indirectness	GRADE Quality
Outcomes under conservative management						
Severe aortic valve calcification **(≥2065 in AU in men and ≥1274 AU in women)** vs non-severe aortic valve calcification (<2065 AU in men and <1274 AU in women) on CT for predicting **mortality under conservative management** Mean follow-up 1.7 years (at least mild AS under conservative management, 27% with heart failure symptoms and mean gradient 35 mmHg; mean age 73 years)	1 (n=794)	Adjusted HR: 1.75 (1.04 to 2.93)[a]	Very serious[b]	None	Serious[c]	VERY LOW
Severe aortic valve calcium **(≥2065 in AU in men and ≥1274 AU in women)** vs non-severe aortic valve calcification (<2065 AU in men and <1274 AU in women) on CT for predicting **death or AVR during follow-up**	1 (n=215)	Adjusted HR: 3.80 (2.16 to 6.69)[d]	Very serious[b]	None	Serious[e]	VERY LOW

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Risk of bias	Imprecision	Indirectness	GRADE Quality
Median follow-up 1029 days (various AS presentations, including mild-severe with symptom status varying between patients; only includes those where decision on whether to perform an intervention had not been made prior to CT in outcome analysis; mean age 77 years)						
Cardiac events (unclear if post-intervention outcomes included)						
Aortic valve calcium score **≥723 vs <723 AU** on CT for predicting **cardiac events** (cardiac death, AVR, non-fatal myocardial infarction and heart failure requiring urgent hospitalisation) Median follow-up 29 months (unadjusted HR estimated from KM curves and number at risk) (asymptomatic mild-severe AS, with 45% being severe cases; mean age 74 years)	1 (n=64)	Unadjusted HR: 6.08 (2.86 to 12.92)[f]	Very serious[b]	None	Very serious[g]	VERY LOW
Aortic valve calcium score **≥723 vs <723 AU** on CT for predicting **non-AVR cardiac events** (cardiac death, non-fatal myocardial infarction and heart failure requiring urgent hospitalisation) Median follow-up 29 months (unadjusted HR estimated from data reported in the paper) (asymptomatic mild-severe AS, with 45% being severe cases; mean age 74 years)	1 (n=64)	Unadjusted HR: 3.69 (1.39 to 9.82)[f]	Very serious[b]	None	Very serious[g]	VERY LOW
Aortic valve calcium score **≥1266 vs <1266 AU** on CT for predicting **cardiac events** (cardiac death, AVR, non-fatal myocardial infarction and heart failure requiring urgent hospitalisation) Median follow-up not reported for asymptomatic severe subgroup (unadjusted HR estimated from KM curves and number at risk)	1 (n=29)	Unadjusted HR: 1.71 (0.71 to 4.13)[h]	Very serious[b]	Serious[i]	Very serious[j]	VERY LOW

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Risk of bias	Imprecision	Indirectness	GRADE Quality
(asymptomatic severe AS subgroup; mean age and other details for this subgroup not reported)						
Aortic valve calcium score **≥1266 vs <1266 AU** on CT for predicting **non-AVR cardiac events** (cardiac death, non-fatal myocardial infarction and heart failure requiring urgent hospitalisation) Median follow-up not reported for asymptomatic severe subgroup (unadjusted HR estimated from KM curves and number at risk) (asymptomatic severe AS subgroup; mean age and other details for this subgroup not reported)	1 (n=29)	Unadjusted HR: 3.08 (0.85 to 11.19)[h]	Very serious[b]	Serious[i]	Very serious[j]	VERY LOW
Post-intervention outcomes						
Calcium score >**6,000 HU vs. ≤6,000 HU** on CT for predicting **all-cause mortality, stroke, myocardial infarction, heart failure or rehospitalisation for cardiac causes** 1 month post-TAVI (undergoing TAVI for AS, >50% NYHA class ≥3 and mean gradient consistent with severe AS; mean age 83.2 years)	1 (n=118)	Adjusted OR: 106.00 (15.44 to 727.53)[k]	Very serious[b]	None	Very serious[l]	VERY LOW
Calcium score **>6,000 HU vs. ≤6,000 HU** on CT for predicting **rehospitalisation** (unclear if all or only cardiac causes) 1 month post-TAVI (undergoing TAVI for AS, >50% NYHA class ≥3 and mean gradient consistent with severe AS; mean age 83.2 years)	1 (n=118)	Adjusted OR: 23.24 (3.59 to 150.38)[k]	Very serious[b]	None	Very serious[m]	VERY LOW
Calcium score **>2027 vs ≤2027 AU** on CT for predicting **mortality post-AVR** 30 days post-AVR (Unadjusted HR estimated from data provided in paper)	1 (n=21)	Unadjusted HR: 1.00 (0.10 to 10.00)[h]	Very serious[b]	serious[i]	Serious[n]	VERY LOW

Risk factor and outcome (population)	**Number of studies**	**Effect (95% CI)**	**Risk of bias**	**Imprecision**	**Indirectness**	**GRADE Quality**
(low-flow low-gradient severe AS undergoing surgical AVR, mean age and further details for the subgroup undergoing surgical AVR unclear)						
Calcium score **≥1200 AU in women and ≥2000 AU in men** on CT for predicting **mortality post-TAVI** 1-year post-TAVI (adjusted HR) (low-gradient severe AS undergoing TAVI, 84% NYHA class III/IV, mean age 82 years)	1 (n=650)	Adjusted HR: 1.32 (0.77 to 2.26)[o]	Very serious[b]	Serious[i]	Serious[p]	VERY LOW
Leaflet calcification **>382 mm^3** on CT for predicting **mortality post-TAVI** 1-year post-TAVI (adjusted HR) (Bicuspid aortic valve undergoing TAVI for symptomatic severe AS, mean age 74.7 (9.3)	1 (n=1034)	Adjusted HR: 2.33 (1.41, 3.85)[q]	Serious[b]	none	Serious[r]	LOW
Aortic valve calcium density tertiles on CT (highest vs other tertiles) for predicting **mortality post-TAVI** 3-year post-TAVI (adjusted HR) (Severe low LVEF low-flow, low-gradient (LFLG) AS undergoing TAVI, median age 79.9 years)	1 (n=290)	Adjusted HR: 0.73 (0.60, 0.88)[s]	Serious[b]	none	Serious[r]	LOW
Aortic valve calcium density tertiles on CT (highest vs other tertiles) for predicting **mortality post-TAVI** 3-year post-TAVI (adjusted HR) (Severe paradoxical LFLG AS undergoing TAVI, median age 82.2 years)	1 (n=236)	Adjusted HR: 0.91 (0.73, 1.14)[t]	Serious[b]	Serious[i]	Serious[r]	VERY LOW
Leaflet calcification **>382 mm^3** on CT for predicting **cardiovascular mortality post-TAVI**	1 (n=1034)	Adjusted HR 2.83 (1.38, 5.81)[q]	Very serious[b]	None	Serious[r]	VERY LOW

Risk factor and outcome (population)	**Number of studies**	**Effect (95% CI)**	**Risk of bias**	**Imprecision**	**Indirectness**	**GRADE Quality**
1-year post-TAVI (adjusted HR) (Bicuspid aortic valve undergoing TAVI for symptomatic severe AS, mean age 74.7 (9.3)						
Severe aortic valve calcium density **(>300 AU/cm^2 for women and >475 AU/cm^2 for men)** compared to no severe aortic valve calcium density on CT for predicting **indication for AVR** during follow-up Median follow-up 27 months (unadjusted HR) (asymptomatic mild-severe AS, mean aortic valve area on echocardiography was 1.01 cm^2; mean age 72 years)	1 (n=115)	Unadjusted HR: 1.0 (1.0 to 1.0)^{u}	Very serious^{b}	None	Very serious^{v}	VERY LOW

(a) *Methods: multivariable analysis, adjusted for age, sex, NYHA class ≥III, diabetes, history of coronary artery disease, indexed aortic valve area, mean gradient and LVEF (includes age but not smoking prespecified in the protocol)*
(b) *Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias*
(c) *Population - unclear whether this represents a population where there was uncertainty about whether or not to intervene as includes mild-severe AS under conservative management*
(d) *Methods: multivariable analysis, adjusted for age, sex Vmax ≥4 m/s and aortic valve area <1.0 cm^2 (includes age but not smoking prespecified in the protocol)*
(e) *Outcome - composite outcome of two separate outcomes listed in the protocol, rather than reporting separately. Also unclear whether AVR captures only unplanned intervention as in our protocol, or whether some were planned procedures following CT results.*
(f) *Methods: no multivariable analysis within this subgroup, unadjusted estimate of HR calculated using data provided in the paper*
(g) *Population - unclear whether represents a population where there is uncertainty about whether or not to intervene, as includes mixture of mild-severe asymptomatic AS with only 45% severe; prognostic factor - threshold is quite different to that specified in the protocol and the same one has been used for men and women, rather than using a separate threshold; and outcome - composite outcome consisting of multiple outcomes listed in the protocol rather than reporting separately.*
(h) *Methods: no multivariable analysis, unadjusted estimate of HR calculated using KM curve and number at risk or other details reported in the paper*
(i) *95% CI crosses null line*
(j) *Prognostic factor - threshold is quite different to that specified in the protocol and the same one has been used for men and women, rather than using a separate threshold; and outcome - composite outcome consisting of multiple outcomes listed in the protocol rather than reporting separately.*
(k) *Methods: multivariable analysis, list of variables included unclear so unclear whether age and smoking prespecified in protocol have been included*
(l) *Population - all had TAVI so already an indication for intervention; prognostic factor - threshold of 6,000 HU used very different to suggested thresholds in protocol and same one used for men and women; and outcome - composite outcome of multiple outcomes in protocol as well as some additional outcomes not listed in protocol*
(m) *Population - all had TAVI so already an indication for intervention; and prognostic factor - threshold of 6,000 HU used very different to suggested thresholds in protocol and same one used for men and women.*
(n) *Prognostic factor - same threshold used for men and women rather than a separate one as in protocol*
(o) *Methods: multivariable analysis adjusted for BMI, GFR, dyslipidaemia, LV hypertrophy, mean pressure gradient, aortic valve area index, balloon expandable valve, rapid pacing, residual AR.*
(p) *Population - all had TAVI so already an indication for intervention*

(q) *Methods: multivariable analysis adjusted for age, STS score, peripheral vascular disease, prior AF, calcified raphe, aortopathy, and non-TF access.*
(r) *Population - all had TAVI so already an indication for intervention; and prognostic factor – calcium density, not calcium score threshold as stated in the protocol*
(s) *Methods: multivariable analysis adjusted for age, BMI, diabetes, COPD, atrial fibrillation, and non-TF access*
(t) *Methods: multivariable analysis adjusted for age, BMI, diabetes, COPD, atrial fibrillation, prior myocardial infarction and non-TF access.*
(u) *Methods: no multivariable analysis, unadjusted HR reported in the paper. May be an error with reporting as confidence interval 1.0-1.0 was the reason it could not be analysed in Revman and GRADE*
(v) *Prognostic factor – calcium density, not calcium score threshold as stated in the protocol*

Aortic regurgitation

Table 8: Clinical evidence summary: aortic regurgitant fraction or volume on cardiac MRI

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Risk of bias	Imprecision	Indirectness	GRADE Quality
Aortic regurgitant fraction						
AR fraction **>33% vs ≤33%** on cardiac MRI for predicting development of an **indication for surgery** during follow-up – mean follow-up 2.6 years (asymptomatic moderate or severe chronic AR; mean age 49 years)	1 (n=113)	Adjusted HR: 7.40 (2.94 to 18.60)[a]	Very serious[b]	None	None	LOW
AR fraction **≥34% vs <34%** on cardiac MRI for predicting **aortic valve surgery** during follow-up – median follow-up 587 days (asymptomatic moderate-severe or severe AR; mean age 44 years)	1 (n=104)	Adjusted HR: 1.05 (1.02 to 1.08)[c]	Very serious[b]	None	None	LOW
Aortic regurgitant volume						
AR volume **>42 ml vs ≤42 ml** on cardiac MRI for predicting development of an **indication for surgery** during follow-up – mean follow-up 2.6 years	1 (n=113)	Adjusted HR: 13.20 (3.80 to 45.80)[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
(asymptomatic moderate or severe chronic AR; mean age 49 years)						
AR fraction **≥45 ml vs <45 ml** on cardiac MRI for predicting aortic valve surgery during follow-up – median follow-up 587 days (asymptomatic moderate-severe or severe AR; mean age 44 years)	1 (n=104)	Adjusted HR: 1.03 (1.02 to 1.04)[c]	Very serious[b]	None	None	LOW

(a) Methods: multivariable analysis, appears to be adjusted for regurgitant volume and LV end-diastolic volume, though this is unclear (does not appear to have adjusted for age which was prespecified in the protocol)

(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, adjusted for MRI-derived LV volumes or their indices (does not appear to have adjusted for age which was prespecified in the protocol)

Mitral regurgitation

Table 9: Clinical evidence summary: Mitral regurgitant volume on cardiac MRI

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Risk of bias	Imprecision	Indirectness	GRADE Quality
Mitral regurgitant volume per 10 mL on cardiac MRI for predicting **mortality** during follow-up Median follow-up 5.0 years (asymptomatic moderate or severe chronic organic MR; mean age 63 years)	1 (n=258)	Adjusted HR: 1.10 (1.05–1.20)[a]	Very serious[b]	None	None	LOW
Mitral regurgitant volume per 10 mL on cardiac MRI for predicting **indication for surgery** during follow-up Median follow-up 5.0 years (asymptomatic moderate or severe chronic organic MR; mean age 63 years)	1 (n=258)	Adjusted HR: 1.23 (1.06–1.29)[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
MR volume **≤55 ml vs. >55 ml** on cardiac MRI for predicting **indication for surgery** during follow-up Mean follow-up 2.5 years (asymptomatic moderate or severe chronic organic MR; mean age 64.8 years)	1 (n=109)	Unadjusted HR: 0.20 (0.09 to 0.45)[c]	Very serious[b]	None	None	LOW

(a) Methods: Adjusted for age, sex, and LVESVI on MRI.

(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: no multivariable analysis, unadjusted HR reported in the paper

Tricuspid regurgitation

Table 10: Clinical evidence summary: Right ventricular function on cardiac MRI

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Risk of bias	Imprecision	Indirectness	GRADE Quality
Cardiac death following TR surgery						
RVEF per 5% higher (continuous variable) on cardiac MRI for predicting cardiac death following TR surgery – follow-up median 57 months (severe isolated functional TR undergoing TR surgery, 54.7% in NYHA class III/IV; mean age 59.3 years)	1 (n=75)	Adjusted HR 0.71 (0.53 to 0.97)[a]	Very serious[b]	None	Serious[c]	VERY LOW
RVEF <46% vs ≥46% on cardiac MRI for predicting cardiac death following TR surgery – follow-up median 57 months (unadjusted HR estimated from data provided) (severe isolated functional TR undergoing TR surgery, 54.7% in NYHA class III/IV; mean age 59.3 years)	1 (n=75)	Unadjusted HR 5.06 (1.56 to 16.46)[d]	Very serious[b]	None	Serious[c]	VERY LOW

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Risk of bias	Imprecision	Indirectness	GRADE Quality
RV-ESVI per 10 ml/m^2 increase (continuous variable) on cardiac MRI for predicting cardiac death following TR surgery – follow-up median 57 months (severe isolated functional TR undergoing TR surgery, 54.7% in NYHA class III/IV; mean age 59.3 years)	1 (n=75)	Adjusted HR 1.18 (1.03 to 1.37)[a]	Very serious[b]	None	Serious[c]	VERY LOW
RV-ESVI ≥76 ml/m^2 vs. <76 ml/m^2 on cardiac MRI for predicting cardiac death following TR surgery – follow-up median 57 months (unadjusted HR estimated from data provided) (severe isolated functional TR undergoing TR surgery, 54.7% in NYHA class III/IV; mean age 59.3 years)	1 (n=75)	Unadjusted HR 0.29 (0.09 to 0.91)[d]	Very serious[b]	None	Serious[c]	VERY LOW
Postoperative cardiac events (cardiac death or unplanned cardiac-related readmission)						
RVEF per 5% higher (continuous variable) on cardiac MRI for predicting postoperative cardiac events (cardiac death or unplanned cardiac-related readmission) following TR surgery – follow-up median 57 months (severe isolated functional TR undergoing TR surgery, 54.7% in NYHA class III/IV; mean age 59.3 years)	1 (n=75)	Adjusted HR 0.8 (0.65 to 0.97)[a]	Very serious[b]	None	Serious[c]	VERY LOW
RVEF <46% vs ≥46% on cardiac MRI for predicting postoperative cardiac events (cardiac death or unplanned cardiac-related readmission) following TR surgery – follow-up median 57 months (unadjusted HR estimated from data provided) (severe isolated functional TR undergoing TR surgery, 54.7% in NYHA class III/IV; mean age 59.3 years)	1 (n=75)	Unadjusted HR 3.94 (1.59 to 9.76)[d]	Very serious[b]	None	Serious[c]	VERY LOW
RV-ESVI per 10 ml/m^2 increase (continuous variable) on cardiac MRI for predicting postoperative cardiac events (cardiac death or unplanned cardiac-related readmission) following TR surgery – follow-up median 57 months	1 (n=75)	Adjusted HR 1.1 (1 to 1.22)[a]	Very serious[b]	Serious[e]	Serious[c]	VERY LOW

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Risk of bias	Imprecision	Indirectness	GRADE Quality
(severe isolated functional TR undergoing TR surgery, 54.7% in NYHA class III/IV; mean age 59.3 years)						
RV-ESVI ≥76 ml/m^2 vs. <76 ml/m^2 on cardiac MRI for predicting postoperative cardiac events (cardiac death or unplanned cardiac-related readmission) following TR surgery – follow-up median 57 months (unadjusted HR estimated from data provided) (severe isolated functional TR undergoing TR surgery, 54.7% in NYHA class III/IV; mean age 59.3 years)	1 (n=75)	Unadjusted HR 0.46 (0.19 to 1.11)[d]	Very serious[b]	Serious[e]	Serious[c]	VERY LOW

(a) Methods: multivariable analysis, adjusted for age, sex, NYHA class, haemoglobin level and glomerular filtration rate

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

(c) Population - all underwent intervention for severe functional TR so does not represent population where there is uncertainty about whether there is an indication for intervention; and outcome - only includes cardiac deaths and not all deaths.

(d) Methods: no multivariable analysis, HR estimated from data provided in paper

(e) 95% CI crossed null line

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.

1.1.8 Summary of included economic evidence

None.

1.1.9 Economic model

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

1.1.10 Unit costs

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

Resource	Unit costs	Source
Outpatient cardiac MRI without contrast	£273	NHS Reference Costs 2018-2019[199]
Outpatient cardiac MRI with post-contrast only	£307	NHS Reference Costs 2018-2019[199]
Outpatient cardiac MRI with pre and post contrast	£392	NHS Reference Costs 2018-2019[199]
Outpatient cardiac CT	£194	NHS Reference Costs 2018-2019[199]

1.1.11 Evidence statements

Effectiveness

See the summary of evidence in Table 7, Table 8, Table 4, Table 5, Table 6, Table 3, Table 9, Table 10 and Table 11.

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

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

- Outcomes following no intervention (medical/conservative treatment):
    - Mortality
    - Hospital attendance/admission for heart failure or unplanned intervention
    - Reduced cardiac function
    - Symptom onset or symptom worsening (e.g. that led to surgery being required)

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

- Outcomes following intervention (transcatheter or surgical treatment):
    - Mortality
    - Hospital admission for heart failure
    - Reduced cardiac function (echo or CMR parameters – for example LVEF <50%)
    - Return to normal LV volumes post-operatively based on echo or CMR as defined in the study
    - >20% reduction in LV volume post-operatively based on echo or CMR

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

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

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

There was no evidence for the outcome of post-operative reduction in left ventricular volume.

1.1.12.2 The quality of the evidence

Strata and risk factors covered

No evidence was identified for the following population strata: mitral stenosis and secondary mitral regurgitation.

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

- Aortic stenosis: 5/10 pre-specified risk factors
  - LVEF on cardiac MRI (3 studies)
  - myocardial fibrosis on cardiac MRI (10 studies)
  - coronary artery disease on CT (3 studies)
  - aortic valve area on CT (1 study)
  - aortic valve calcium score on CT (9 studies)
- Aortic regurgitation: 1/8 pre-specified risk factors
  - regurgitant fraction and regurgitant volume on cardiac MRI (2 studies)
- Primary mitral regurgitation: 1/5 pre-specified risk factors
  - regurgitant volume on cardiac MRI (2 studies)
- Functional tricuspid regurgitation: 1/4 pre-specified risk factors
  - right ventricular systolic function on cardiac MRI (1 study)

Quality and limitations

The quality of the evidence was low to very low for most analyses. One outcome, reporting mortality under medical management in the section of evidence for aortic valve area measured on cardiac CT in adults with aortic stenosis was rated as moderate quality, with only minor risk of bias limitations. The main reason for downgrading in all studies was risk of bias, commonly because of limitations in the adjustment for confounding and statistical analysis – many studies did not perform multivariable analysis, while some studies that did use multivariable analysis the covariates included were unclear.

For many of the studies, indirectness relative to the protocol was also a reason for downgrading. For example, many studies only included people who already had an indication for surgery. In a few studies, outcome indirectness was considered to be present. This was because they had included medically and surgically treated patients in the analysis and had not adjusted for this or censored at the time of surgery, meaning separate outcomes were not available for those that did not receive intervention and those that received intervention. The committee agreed that despite this indirectness the evidence was important to include, while noting the limitations when discussing the findings. This was because they were aware of very few studies where CT or MRI were used strictly in those where the need for intervention was unclear and agreed that it is better to extrapolate from indirect evidence, when appropriate, than to rely on their experience alone.

Although some studies reported similar risk factors in similar populations, pooling was only performed in one analysis. This was because in all other cases there were differences between the studies in population, prognostic factor definition or the outcome reported.

Another limitation of the evidence was the size of the studies, with most including fewer than 300 participants. Therefore, the results were based on small populations and imprecision caused uncertainty in the true size of the effect.

It is important to note that although this review aims to assess which risk factors measured on cardiac CT or cardiac MRI indicate that intervention should be performed in various valve disease presentations, this is based on interpretation of outcomes with and without intervention. For example, if a particular risk factor appears to be associated with a worse outcome (e.g. higher mortality) on medical treatment compared to those without the risk factor, this may mean that intervention should be considered for those with this risk factor.

However, unless sufficient separate information is available for the same risk factor in populations that received medical treatment/conservative management and populations that received surgical treatment, it is difficult to be sure that surgery would improve the prognosis of those with the risk factor, as the risk factor could worsen the prognosis of all patients, regardless of whether medical treatment or intervention is selected. To make strong conclusions about whether intervention would improve the prognosis of people with particular risk factors, evidence comparing medical treatment and intervention within these subgroups would be required, which is not addressed by this review. However, the committee agreed that groups that experience poor outcomes following surgery are likely to experience even poorer outcomes if only medical management is provided, as these prognostic groups are associated with poorer outcome compared to those without the prognostic factor, regardless of which treatment is performed, although it was agreed that surgery would be a better option in these patients if suitable. Evidence of a prognostic factor being associated with a negative outcome following medical, transcatheter or surgical treatment was therefore used to support it as an indicator for intervention, as the committee agreed that intervention would improve outcomes compared to medical management for patients within these groups associated with poorer prognosis.

Based on a combination of the limitations reported above, all recommendations of indications for intervention were consider recommendations as there was insufficient evidence to support making offer recommendations. In addition, for some prognostic factors, although there was some evidence suggesting a role as a prognostic factor for worse outcome, the evidence was insufficient to make any active recommendation because of the low quality and uncertainty due to imprecise estimates.

1.1.12.3 Benefits and harms

The committee highlighted that all of the evidence was limited to showing whether the imaging parameters are associated with an adverse prognosis, but evidence about how intervention would impact this poor outcome is lacking.

Aortic stenosis

Left ventricular ejection fraction on cardiac MRI

Three small studies in people scheduled for aortic valve intervention or TAVI suggested a possible increased risk of mortality after intervention at an average of 2-4 years follow-up among those with baseline LVEF <50%, however, there was uncertainty in the effect estimates. Therefore, a research recommendation was made in this area (see Appendix K.1.11 for details).

Myocardial fibrosis on cardiac MRI

Ten studies investigated myocardial fibrosis, considering midwall fibrosis late gadolinium enhancement (LGE) pattern, any LGE pattern or any myocardial fibrosis in people with aortic stenosis. One study showed an increased risk of all-cause mortality at 2 years in those with midwall LGE pattern compared to no LGE on cardiac MRI and another study showed an increased risk of all-cause mortality at 10 years in those with severe fibrosis compared to no fibrosis on cardiac MRI. These same two studies also investigated infarct fibrosis LGE pattern compared to no LGE and mild fibrosis compared to no fibrosis on cardiac MRI, respectively. Although the direction of effect suggested an increased risk of poor outcomes for those with infarct fibrosis or with mild fibrosis compared to those with no fibrosis, there was large uncertainty around these effects and the size of the increased risk was smaller than for midwall or severe fibrosis.

Four small studies comparing those with and without late gadolinium enhancement or myocardial fibrosis on cardiac MRI reported composite outcomes, all of which included mortality. There was variation in the populations included as well as the outcome definitions. However, the majority suggested that myocardial fibrosis was associated with increased risk of a poor outcome. It was noted that the proportions of those with mid-wall fibrosis among those positive for LGE/fibrosis differed between the studies and was not always stated.

Four studies reported on outcomes after intervention. One pooled analysis showed an increased risk of all-cause mortality at approximately 3 years post intervention in those with late gadolinium enhancement on cardiac MRI at baseline assessment. Similarly, one of these studies also showed an increased risk of cardiovascular mortality post-intervention. One further study demonstrated that compared to a normal myocardium, diffuse myocardial fibrosis was associated with an increased risk of poor outcome after aortic valve replacement.

The experience of the committee was in line with these findings, as they were aware that myocardial fibrosis in general, not necessarily in aortic stenosis, is associated with a worse prognosis. Futhermore, myocardial fibrosis in people with aortic stenosis indicates early decompensation and the possible need for early intervention to stop progression, because midwall fibrosis cannot be reversed or improved by intervention. Midwall fibrosis was discussed as being seen to confer a particularly high need for intervention to avoid mortality. Therefore, based on the experience of the committee and the clinical evidence, it was agreed that follow-up should be enhanced in those with midwall fibrosis to check for symptoms and enable earlier aortic valve intervention to improve prognosis. It was noted that, cardiac MRI is indicated for various reasons, and this recommendation does not dictate if or when MRI should be performed, but rather advises on how to act upon the result of an MRI performed in a patient with aortic stenosis. Examples of enhanced follow up include review at shorter time intervals and / or referral for exercise echocardiography to unmask symptoms or other prognostic parameters that would indicate referral for surgery.

Coronary artery disease on cardiac CT

There was evidence from 2 patient cohorts showing a trend towards an increased risk of cardiac events or needing aortic valve intervention among those with coronary artery disease. However, there was uncertainty in the findings and insufficient evidence to inform a recommendation. The committee agreed not to prioritise this as an area for a research recommendation because coronary angiography is a more appropriate test.

Aortic valve area on cardiac CT

One study showed that an aortic valve area ≤1.2 cm^2 predicted an increased risk of mortality under medical management, while there was no clear increased risk when the threshold was set as ≤1.0 cm^2. This single study was insufficient evidence to inform a recommendation, especially as it conflicts with a larger body of evidence from echocardiography that an aortic valve area of ≤1.0 cm^2 is the most useful prognostic indicator and because this threshold is not used in current practice. However, no research recommendation was made in this area because measurement of aortic valve area is established using echocardiography and the committee agreed measurement on CT was not a research priority. Recommendations about the use of aortic valve area measured on echocardiography have been made based on evidence in review D.

Aortic valve calcium score on cardiac CT

There was evidence from two studies that a high aortic valve calcium score (≥2065 AU in men and ≥1274 AU in women) is a predictor of poor outcome in terms of mortality under conservative management or death or need for aortic valve intervention during follow-up. Regarding post-operative outcomes, there was evidence from one study of a very large increase in risk of the composite outcome of all-cause mortality, stroke, myocardial infarction, heart failure or rehospitalisation for cardiac causes after TAVI and a large increased risk of rehospitalisation in those with a calcium score of >6000 HU. The committee noted that in low gradient aortic stenosis, a high calcium score or calcium density was not clearly associated with poor outcome after surgery, while this association was seen in bicuspid aortic stenosis. It was discussed that in the low-flow, low gradient population the evidence of those with higher calcium having a more positive prognosis after intervention could reflect the increased benefit of TAVI in this group and so favouring the use of calcium score to stratify for intervention. The committee acknowledged that there was currently insufficient evidence to specify precise CT calcium score thresholds that indicate referral. However, the committee agreed that the available evidence demonstrates that a higher aortic valve calcium score measured on cardiac CT is a marker for worse prognosis, which could be because it is an index of the severity of stenosis or a marker of more widespread vascular disease. This was supported by the knowledge and experience of the committee, who noted that a more calcified aortic valve is associated with more severe aortic stenosis. However, this does not apply in the same way to bicuspid aortic valves or rheumatic disease, because the mechanism of aortic stenosis is different and it would not be as relevant to monitor valve calcium. Therefore, the committee agreed that aortic valve calcium scoring is useful to assess the need for intervention in adults with symptomatic aortic stenosis of uncertain severity. This was because a high calcium score is likely to reflect more severe disease with a worse prognosis that, if symptomatic, may require intervention as in severe aortic stenosis the symptoms are more likely to be due to the heart valve disease. The committee agreed that this would also apply to those with low-flow, low gradient aortic stenosis because in their experience, calcium scoring is used to assess severity in these cases and the evidence did not reflect the appropriate population of those with uncertain severity.

Additionally, based on their expert opinion and the evidence of a worse prognosis after TAVI among those with a very high calcium score (large increased risk of rehospitalisation, or the composite of all-cause mortality, stroke, myocardial infarction, heart failure or rehospitalisation for cardiac causes in those with calcium score >6000 HU), the committee recommended that the amount and distribution of calcium in the aortic valve should be taken into account as part of the decision-making process between surgical and transcatheter intervention. This is because, for example, a very high calcium score may make TAVI a riskier procedure because surgical intervention provides a means to remove the excess calcium that is not possible with transcatheter intervention. In these cases surgical intervention may be considered in preference to TAVI. Regarding the distribution of the calcium, it was acknowledged that calcium in the left ventricular outflow tract may increase the risk of a TAVI procedure. It was agreed that this use of aortic valve calcium score was in line with current practice, as it is commonly used as a discriminator when deciding on the need for intervention. In conclusion, as the degree and distribution of calcium should be considered when deciding if TAVI is appropriate this was covered by recommendation 1.5.4.

Aortic regurgitation

<u>Regurgitant fraction or volume on cardiac MRI</u>

Two studies showed an increased risk of needing surgery among those with AR fraction >33 or ≥34% or AR volume >42 ml or ≥45 ml in asymptomatic moderate or severe AR. However, the committee noted that although the two studies used similar thresholds, the evidence was of low quality and while one showed a large effect the other showed a small effect size. Therefore, there was too much uncertainty in the predictive value of this parameter to make an active recommendation. Also, the threshold for referral or intervention is not well established in current practice and there was no evidence for regurgitant volume, which may also have prognostic value. Therefore, a research recommendation was made in this area (see Appendix K.1.1 for details).

A further research recommendation to assess the prognostic value of left ventricular ejection fraction measured on cardiac MRI was made due to no evidence being identified for this prognostic factor in this population (see Appendix K.1.5 for details).

Mitral regurgitation

<u>Mitral regurgitant volume on cardiac MRI</u>

Two studies showed a better prognosis among those with asymptomatic moderate or severe mitral regurgitation and a lower mitral regurgitant volume. Specifically, one study reported a reduced risk of developing an indication for surgery among those with mitral regurgitant volume ≤55 ml and the other showed that the risk of all-cause mortality or of developing an indication for surgery increases per 10 mL increase of mitral regurgitant volume on cardiac MRI. This evidence was insufficient to support any recommendations that may change practice because it was rated at low quality, only one used dichotomous analysis to inform what threshold may be suitable as an indicator and MRI is not commonly requested for this patient group in current practice. Therefore, a research recommendation was made in this area (see Appendix K.1.1 for details). This research recommendation also covered regurgitant fraction on cardiac MRI as no evidence was identified for this variable in mitral regurgitation.

A further research recommendation to assess the prognostic value of left ventricular ejection fraction measured on cardiac MRI was made due to no evidence being identified for this prognostic factor in this population (see Appendix K.1.5 for details).

Tricuspid regurgitation

Right ventricular function on cardiac MRI

One small study found an increased risk of cardiac death after surgery for tricuspid regurgitation in those with reduced right ventricular function as measured by a higher right ventricular end systolic volume index or a lower right ventricular ejection fraction.

The same trend was seen for the outcome of post-operative cardiac events, although the size of the increased risk was smaller and the uncertainty in the effect was greater than for the mortality outcome. However, this evidence of very low quality was insufficient to support any recommendations.

Due to this limited evidence for right ventricular function in the prognosis of tricuspid regurgitation, a research recommendation was made to assess the prognostic value of right ventricular ejection fraction measured on cardiac MRI (see Appendix K.1.15 for details).

1.1.12.4 Cost effectiveness and resource use

There was no published evidence of cost effectiveness. The committee were presented with the unit costs of cardiac MRI and cardiac CT.

Three consensus recommendations in line with current practice were made to consider aortic valve calcium scoring and distribution and mid-wall fibrosis when determining the need of reintervention in adults with aortic stenosis. The committee agreed that there was not enough robust evidence to specify levels of threshold of calcium score. High aortic valve calcium score was found to be associated with poor prognosis. Hence, the committee recommended to evaluate the need of intervention taking into account the score of aortic valve calcium measured on cardiac CT when the severity of aortic stenosis is uncertain. This could increase the number of interventions performed on patients who can better benefit from it, leading to better health outcomes. The cost effectiveness of CT in this population is uncertain and therefore the committee made a weak ‘consider’ recommendation for CT scanning in this patient group.

The committee aknowledged that aortic calcium score was an important factor in deciding whether to consider TAVI or a surgery as the degree and distribution of calcium in the aortic valve may increase the risk of a TAVI procedure. Hence, the committee recommended to take into account those factors when deciding the appropriate intervention. However, the economic modelling of TAVI – see Evidence Report H – did not show TAVI to be cost effective in surgically operable patients.

1.1.13 Recommendations supported by this evidence review

This evidence review supports recommendations 1.3.4-1.3.6 and 4 research recommendations on cardiac MRI to determine the need for intervention.

1.1.14 References

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Appendices

Appendix A – Review protocols

Review protocol for cardiac MRI and CT in determining the need for intervention

ID	Field	Content
0.	PROSPERO registration number	CRD42020182863
1.	Review title	In adults with heart valve disease, what is the prognostic value and cost effectiveness of cardiac MRI and cardiac CT to determine the need for intervention?
2.	Review question	In adults with heart valve disease, what is the prognostic value and cost effectiveness of cardiac MRI and cardiac CT to determine the need for intervention?
3.	Objective	To assess the prognostic value of cardiac MRI and cardiac CT to determine the need for intervention in adults with diagnosed heart valve disease.
4.	Searches	The following databases (from inception) will be searched: • Embase • MEDLINE Searches will be restricted by: • English language • Human studies • Letters and comments are excluded • Date: exclude studies published before the year 1985 (for MR), and 1995 (for CT)

		Other searches: • Inclusion lists of relevant systematic reviews will be checked by the reviewer. The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review.
5.	Condition or domain being studied	Diagnosed heart valve disease in adults aged 18 years and over: Aortic (including bicuspid) stenosis, aortic (including bicuspid) regurgitation, mitral stenosis, mitral regurgitation and tricuspid regurgitation.
6.	Population	Inclusion: Adults aged 18 years and over with diagnosed heart valve disease **requiring further tests** after echocardiography to determine whether intervention is needed. Data will be stratified by the type of heart valve disease as follows: • aortic [including bicuspid] stenosis • aortic [including bicuspid] 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. Adults with previous intervention for HVD (surgical or transcatheter).
7.	Predictors/prognostic factors of need for intervention	**A. Cardiac MRI** **Mitral regurgitation** **Primary mitral regurgitation** • left ventricular systolic function based on ejection fraction <50% or <60% • left atrial dimensions (volume / volume index) ≥60 mL/m^2 BSA • Quantity of MR (regurgitant fraction or volume in ml – no accepted threshold, suggestion RF 40 or 50% and RV of 55 or 60 ml) **Secondary mitral regurgitation** • left ventricular systolic function based on ejection fraction <20% **Aortic stenosis** • left ventricular systolic function based on ejection fraction <50% or <60% • Myocardial fibrosis (late gadolinium enhancement) (present or not in a pattern consistent with aortic stenosis, or infarction) • Aortic valve area (<0.6cm^2/m^2 or <0.8 or 1.0 cm^2) **Aortic regurgitation** • left ventricular systolic function based on ejection fraction <50% or <60% • Quantity of AR (regurgitant fraction or volume in ml – no accepted threshold, suggestion RF 30 or 40% and RV of 55 or 60 ml) • Presence of holodiastolic flow reversal in the descending aorta

		Mitral stenosis • Valve area by direct planimetry <1.0cm^2 **Tricuspid regurgitation (isolated)** • reduced right ventricular systolic function – no thresholds • increasing right ventricular dimensions – no thresholds (dilated – mild, moderate, severe) • Regurgitant orifice area **B. Aortic size on cardiac MRI or CT** **Aortic stenosis or aortic regurgitation** • Bicuspid: aorta > 5cm or > 5.5cm • Tricuspid: aorta > 5.5cm **C. Cardiac CT** **Primary or secondary mitral regurgitation** • CT coronary angiogram: mild, moderate, or severe coronary disease of 1,2 or 3 vessels • Severity of mitral annular calcification (mild, moderate, severe) **Aortic stenosis** • CT coronary angiogram: mild, moderate, or severe coronary disease of 1,2 or 3 vessels • Aortic valve area (<0.6cm^2/m^2 or <0.8 or 1.0 cm^2) • Calcium score of aortic valve (threshold > 2000 AU for men and >1200 AU for women) **Aortic regurgitation** • CT coronary angiogram: mild, moderate, or severe coronary disease of 1,2 or 3 vessels **Mitral stenosis**

		• CT coronary angiogram: mild, moderate, or severe coronary disease of 1,2 or 3 vessels • Valve area by direct planimetry <1.0cm^2 • Severity of mitral valve or annular calcification (mild, moderate, severe) **Tricuspid regurgitation** • CT coronary angiogram: mild, moderate, or severe coronary disease of 1,2 or 3 vessels
8.	Confounding factors	For non-operative mortality • Age • Smoking For hospital admission for heart failure or unplanned intervention and for reduced cardiac function in those without intervention: • Age For post-operative mortality: • Age For all outcomes relating to cardiac calcium score in patients with aortic stenosis: • Age • Smoking For all other outcomes • No known confounders
9.	Types of study to be included	• Prospective and retrospective cohort studies that control for confounders in the study design or analysis will be included preferentially

		• If no controlled studies are identified, unadjusted cohort studies will be considered for inclusion. This will be assessed separately for each test and population. • Systematic reviews of the above • If no cohort studies are identified case control studies will be considered for inclusion, but downgraded for risk of bias. This will be assessed separately for each test and population.
10.	Other exclusion criteria	Exclusion criteria: • Conference abstracts will be excluded because they are unlikely to contain enough information to assess whether the population matches the review question in terms of previous medication use, or enough detail on outcome definitions, or on the methodology to assess the risk of bias of the study. • Non-English language studies
11.	Context	Among adults with diagnosed heart valve disease who have had an initial echocardiography assessment, some require further tests to determine if intervention is needed. CT and MRI may be used in this population to provide additional information on the severity of the disease.
12.	Primary outcomes (critical outcomes)	Indication for intervention based on prognosis for the following without intervention: • Mortality (1 and 5 years) • Hospital admission for heart failure or unplanned intervention (1 and 5 years) • Reduced cardiac function (echo parameters – LVEF) 1 and 5 years • Symptom onset or symptom worsening (e.g. that led to surgery being required) 1 and 5 years Indication for intervention based on predictors of the following post-operative outcomes: • Mortality (6 and 12 months) • Hospital admission for heart failure (6 and 12 months)

		• Reduced cardiac function (echo or CMR parameters – for example LVEF <50%) (6 and 12 months) • Return to normal LV volumes post-operatively based on echo or CMR as defined in the study (6 and 12 months) • >20% reduction in LV volume post-operatively based on echo or CMR (6 and 12 months) This may be reported as an adjusted HR, RR or OR. Sensitivity, specificity and AUC will not be included as these do not allow for multivariable adjustment. Use the time point closest to each of the listed endpoints and combine data as follows: 6 months: include 0-6 months 12 months: include >6 months up to 12 months 1 year: include 0-12 months 5 years: include all >1 year. No minimum follow-up.
13.	Secondary outcomes (important outcomes)	N/A
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 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

<table>
<tr><td></td><td></td><td colspan="2">and imprecision) will be appraised for each risk factor. Publication or other bias will be tested for when there are 5 or more studies for an outcome.
• Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic. We will consider an I^2 value greater than 50% indicative of substantial heterogeneity. We will conduct sensitivity analyses based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented using random-effects.
• If meta-analysis is not possible or appropriate, results will be reported individually per outcome in adapted GRADE tables.

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).</td></tr>
<tr><td>17.</td><td>Analysis of sub-groups</td><td colspan="2">Groups that will be analysed separately (strata):

Stratified by the presence or absence of symptoms and the type of heart valve disease as follows:

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:
• none identified</td></tr>
<tr><td>18.</td><td>Type and method of review</td><td>☐</td><td>Intervention</td></tr>
</table>

		☐	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; cardiac computerised tomography; cardiac magnetic resonance imaging; diagnosis; heart valve disease; mitral regurgitation; mitral stenosis; prognosis; 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	

Table 11: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2004, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[196] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).

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

Appendix B – Literature search strategies

Heart valve disease – search strategy 4 – Cardiac CT and cardiac MRI indications for intervention

This literature search strategy was used for the following review:

- In adults with heart valve disease, what is the prognostic value and cost effectiveness of cardiac MRI and cardiac CT to determine the need for intervention?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[196]

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

B.1 Clinical search literature search strategy

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

Table 12: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1995 - 14 October 2020	Exclusions
Embase (OVID)	1995 - 14 October 2020	Exclusions

Medline (Ovid) search terms

1.	exp Heart Valve Diseases/
2.	exp heart valves/
3.	((primary or secondary) adj valv* disease*).ti,ab.
4.	((valv* or flap* or leaflet*) adj1 (heart or cardiac) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)).ti,ab.
5.	((mitral or aortic or tricuspid or pulmon*) adj (valv* or flap* or leaflet*) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)).ti,ab.
6.	((mitral or aortic or tricuspid or pulmon*) adj3 (prolapse or regurgitation or stenos?s or atresia or insufficienc*)).ti,ab.
7.	exp Heart Murmurs/
8.	((heart or cardiac) adj murmur*).ti,ab.
9.	or/1-8
10.	letter/
11.	editorial/
12.	news/
13.	exp historical article/
14.	Anecdotes as Topic/
15.	comment/
16.	case report/
17.	(letter or comment*).ti.
18.	or/10-17
19.	randomized controlled trial/ or random*.ti,ab.
20.	18 not 19
21.	animals/ not humans/
22.	exp Animals, Laboratory/
23.	exp Animal Experimentation/
24.	exp Models, Animal/
25.	exp Rodentia/
26.	(rat or rats or mouse or mice).ti.
27.	or/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.	Magnetic Resonance Imaging/
33.	magnetic resonance angiography/
34.	(mri* or nmr* or magnetic resonance).ti,ab.
35.	(cmr or ((cardiac or cardiovascular) adj mr)).ti,ab.
36.	tomography, x-ray computed/ or computed tomography angiography/
37.	((x-ray or radiograph* or compute*) adj3 tomograph*).ti,ab.
38.	Coronary Angiography/ and (compute* or ct or tomograph*).ti,ab.
39.	((compute* or ct or tomograph*) adj3 angiograph*).ti,ab.
40.	((heart or cardiac or myocardial or imag* or scan* or diagnos*) adj2 (ct or cat)).ti,ab.
41.	(cta or ccta or tro-cta or msct).ti,ab.
42.	or/32-41
43.	31 and 42

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.	limit 26 to English language
28.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
29.	27 not 28
30.	nuclear magnetic resonance imaging/ or magnetic resonance angiography/
31.	(mri* or nmr* or magnetic resonance).ti,ab.
32.	(cmr or ((cardiac or cardiovascular) adj mr)).ti,ab.
33.	computed tomographic angiography/
34.	x-ray computed tomography/
35.	tomography, x-ray computed/ or computed tomography angiography/
36.	((x-ray or radiograph* or compute*) adj3 tomograph*).ti,ab.
37.	coronary angiography/ and (compute* or ct or tomograph*).ti,ab.
38.	((compute* or ct or tomograph*) adj3 angiograph*).ti,ab.
39.	((heart or cardiac or myocardial or imag* or scan* or diagnos*) adj2 (ct or cat)).ti,ab.
40.	(cta or ccta or tro-cta or msct).ti,ab.
41.	or/30-40
42.	29 and 41

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 13: 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/

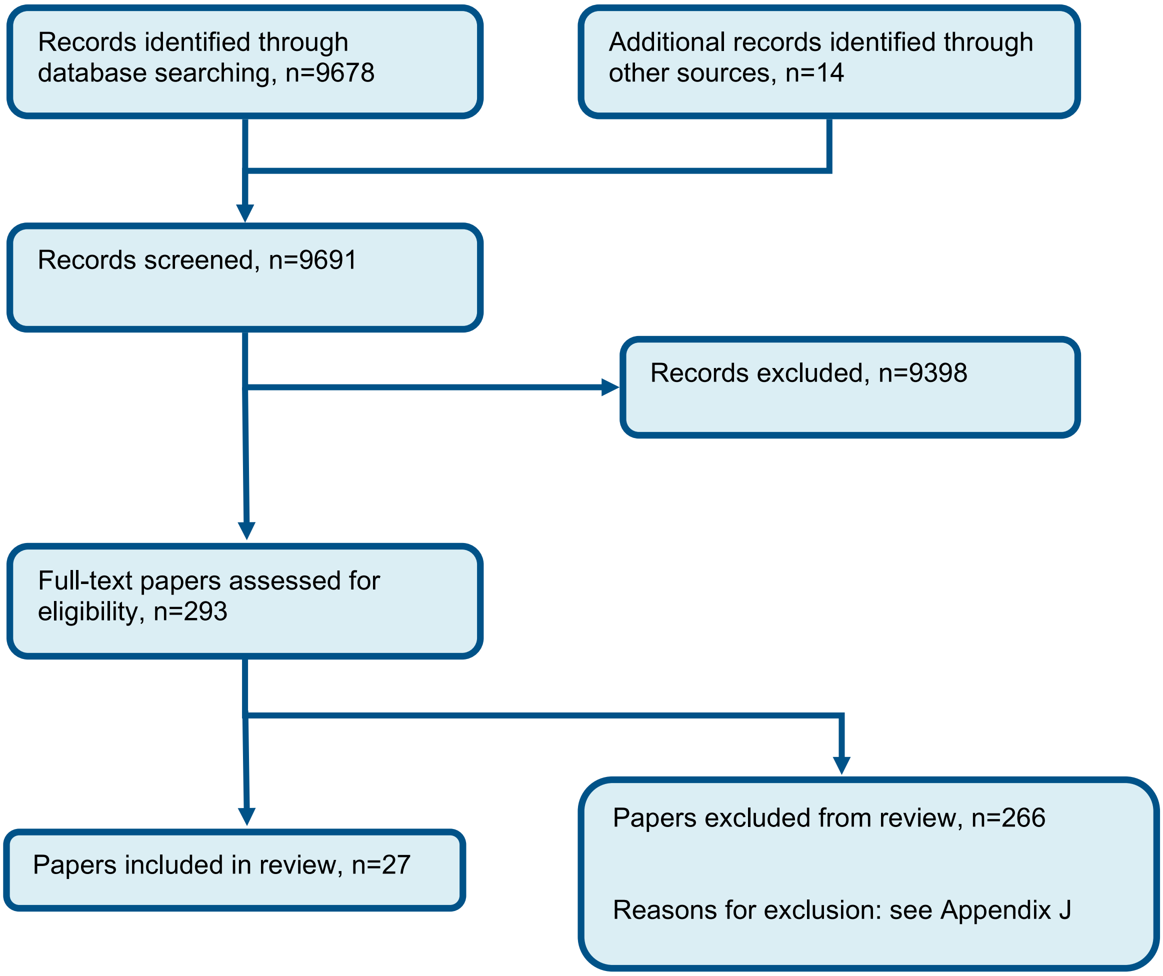
35.	exp economic evaluation/
36.	exp health care cost/
37.	exp fee/
38.	budget/
39.	funding/
40.	budget*.ti,ab.
41.	cost*.ti.
42.	(economic* or pharmaco?economic*).ti.
43.	(price* or pricing*).ti,ab.
44.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
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 cardiac MRI and CT in determining the need for intervention



Appendix D – Prognostic evidence

D.1 Aortic stenosis – left ventricular ejection fraction (LVEF) on CMR

Reference	Everett 2020[88]
Study type and analysis	Data from multiple prospective cohort studies combined Multivariate Cox regression model UK, Germany, USA, Canada and South Korea
Number of participants and characteristics	N=440 LV ejection fraction (LVEF) <50% on CMR, n=71 LVEF ≥50% on CMR, n=369 Severe aortic stenosis (AS) scheduled for aortic valve intervention. Population indirectness as considered to be an indication for intervention in all patients already, prior to cardiac magnetic resonance (CMR) imaging. Aortic valve intervention was performed at a median of 15 (IQR, 4-58) days following CMR. This was isolated surgical aortic valve replacement (AVR) in n=311 (71%), combined coronary artery bypass grafting with surgical AVR in n=62 (14%) and transcatheter AVR in n=67 (15%). **Inclusion criteria:** Severe AS scheduled for aortic valve intervention. **Exclusion criteria:** Presence of an implantable cardiac device; advanced renal dysfunction (estimated glomerular filtration rate <30 ml/min/1.73 m^2; previous valve replacement; presence of another co-existent myocardial pathology (e.g. cardiac amyloidosis, hypertrophic cardiomyopathy or myocarditis); unable to analyse T1 maps.

Reference	Everett 2020[88]
	Values listed below are presented as mean (SD) or number (%) • Age: 69.67 (10.11) years • Male/female: 259/181 (59%/41%) • Body mass index: 27.60 (5.06) kg/m^2 • Body surface area: 1.85 (0.24) m^2 • Hypertension, 280 (64%) • Diabetes mellitus, 93 (21%) • Atrial fibrillation, 56 (13%) • Previous myocardial infarction, 38 (9%) • Coronary artery disease, 168 (38%) • NYHA functional class III/IV, 157 (36%) • Systolic blood pressure: 130.7 (19.84) mmHg • Diastolic blood pressure: 72.67 (12.04) mmHg • STS-PROM score, median (IQR): 1.44 (0.88-2.29)%, 1.40 (0.92-2.15)% and 1.89 (1.13-3.31)% in tertiles of extracellular volume fraction <25.9%, 25.9%-29.1% and >29.1%, respectively. • EuroSCORE II, median (IQR): 1.24 (0.82-2.19)%, 1.44 (0.99-2.21)% and 2.18 (1.14-4.28)% in tertiles of extracellular volume fraction <25.9%, 25.9%-29.1% and >29.1%, respectively. • Peak aortic jet velocity: 4.46 (0.80) m/s • Peak aortic valve gradient: 81.99 (29.68) mmHg • Mean aortic valve gradient: 49.66 (18.82) mmHg • Aortic valve area: 0.73 (0.25) cm^2 • Indexed aortic valve area: 0.40 (0.13) cm^2/m^2 • Valvuloarterial impedance: 3.92 (1.12) mmHg/ml/m^2 • Bicuspid aortic valve, 144 (33%) • Indexed LV end-diastolic volume: 78.33 (28.30) ml/m^2 • Indexed LV end-systolic volume, median (IQR): 17 (11-28) ml/m^2, 21 (14-36) ml/m^2 and 30 (17-51) ml/m^2 in tertiles of extracellular volume fraction <25.9%, 25.9%-29.1% and >29.1%, respectively. • Indexed LV stroke volume: 49 (13.49) ml/m^2

Reference	Everett 2020[88]
	- LV ejection fraction: 66 (16.37)% - LV ejection fraction <50%, 71 (16%) - LV mass index: 93.33 (32.31) g/m^2 - Indexed RV end-diastolic volume: 65 (18.13) ml/m^2 - Indexed RV end-systolic volume, median (IQR): 21 (16-27) ml/m^2, 21 (15-29) ml/m^2 and 23 (16-30) ml/m^2 in tertiles of extracellular volume fraction <25.9%, 25.9%-29.1% and >29.1%, respectively. - Indexed RV stroke volume: 41.33 (10.69) ml/m^2 - RV ejection fraction: 64 (10.9)% - Indexed left atrial volume: 53.33 (23.1) ml/m^2 - LGE, 220 (50%) **Population source:** patients matching inclusion criteria from multiple prospective observational cohorts (10 centres across Europe, North America and Asia).
Prognostic variable	LVEF <50% on CMR LVEF ≥50% on CMR (referent) All underwent CMR with T1 mapping performed prior to and following intravenous gadolinium contrast administration. Range of different scanners used across centres. Different T1 mapping pulse sequences and field strengths were also used. Standard long-axis cine images were obtained as well as a short-axis cine stack of the left ventricle. LGE imaging with short axis left ventricle stack and standard long-axis views performed 5-15 min after gadolinium was administered. T1 mapping data acquired in short-axis mid-ventricular view of left ventricle before and 10-20 min following gadolinium administration. CMR image analysis performed by two operators within a core lab according to standardised protocol. Operators were blinded to outcome data. Presence of midwall and infarct patterns of LGE recorded and quantitative analysis performed using full-width-at-half-maximum technique. Extent of LGE expressed as percentage of total LV mass. Areas of signal contamination by epicardial fat or blood pool were manually excluded. LVEF was calculated by contouring the short-axis stack
Confounders	Multivariate Cox regression model. Variables with a significant association on univariate analysis were included in the multivariate model. Factors included in adjusted analysis: extracellular volume percentage, age, gender, LV ejection fraction <50%, LGE on CMR and peak aortic jet velocity. Though two models with different variables included were reported, the results from the model with the highest number of factors included were extracted. The only difference between the two models was the inclusion of peak aortic jet velocity in the model that has been extracted, which was not included in the other reported model.

Reference	Everett 2020[88]
	Age was the confounder prespecified in the protocol for this outcome and has been included in the multivariate model.
Outcomes and effect sizes	**<u>All-cause mortality following aortic valve intervention</u>** **HR 1.527 (95% CI 0.761 to 3.064) for LVEF <50% on CMR vs. ≥50% on CMR** During follow-up, 52 deaths occurred. Of these, 7 occurred within 30 days of valve intervention (1 perioperative death). Robust cause of death data was available in 37 cases (71%) and 14 of these (38%) were considered to be cardiovascular deaths. The primary outcome was all-cause mortality. Cardiovascular mortality was defined as death due to myocardial ischaemic or infarction, heart failure, cardiac arrest (due to arrhythmia or unknown cause) or cerebrovascular accident. Outcome events were adjudicated by review of patient health records (including U.K. Spine database) and cause of death was adjudicated by three observers. For centres in the UK, death certificates were available for all patients. Deaths occurring at international sites outside of the UK were adjudicated using a combination of medical record review, reports from family members and death certificates. No multivariate results were provided for cardiovascular mortality. Median (IQR) follow-up: 3.8 (2.8-4.6) years. Final status checks were performed between January and August 2018 and no patient was lost to follow-up.
Comments	**<u>All-cause mortality following aortic valve intervention</u>** <u>LVEF <50% vs. LVEF ≥50% on CMR</u> Risk of bias: 1. Study participation LOW 2. Study attrition LOW 3. Prognostic factor measurement HIGH 4. Outcome Measurement LOW 5. Study confounding LOW 6. Statistical analysis HIGH 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH Indirectness:

Reference	**Everett 2020[88]**
	• Population – all already scheduled for aortic valve intervention so no uncertainty about whether there is indication for intervention.

Reference	**Hwang 2020[123] (also reported above for CMR myocardial fibrosis)**
Study type and analysis	Prospective cohort study Univariate regression analysis for LVEF South Korea
Number of participants and characteristics	N=43 (numbers in each group not reported) LVEF <50% on cardiac MRI LVEF ≥50% on cardiac MRI (referent) Severe aortic stenosis (AS) scheduled for isolated aortic valve replacement (AVR). Population indirectness as already indication for intervention and not within a population where there is uncertainty. **Inclusion criteria:** Severe AS scheduled for isolated AVR (without coronary artery bypass grafting). **Exclusion criteria:** Moderate or greater degree of other valve disease types; contraindications to CMR; prior cardiac surgery or myocardial infarction; patients where T1 mapping was not performed. **Values listed below are presented as mean (SD) or number (%)** • Age: 65.9 (8.1) years • Male/female: 24/19 (55.8%/44.2%) • Hypertension, 24 (55.8%) • Diabetes mellitus, 7 (16.3%) • Dyslipidaemia, 9 (20.9%) • Atrial fibrillation, 7 (16.3%) • Prior percutaneous coronary intervention, 3 (7.0%) • Bicuspid aortic valve, 19 (44.2%) • Current smoker, 3 (7.0%)

Reference	Hwang 2020[123] (also reported above for CMR myocardial fibrosis)
	• EuroSCORE II: 1.50 (0.87)% • Systolic blood pressure: 121.0 (18.3) mmHg • Diastolic blood pressure: 71.2 (10.4) mmHg • NYHA functional class: 2.1 (0.8) • Chest pain, 12 (27.9%) • Syncope, 6 (14.0%) • Haemoglobin: 13.6 (1.7) g/dL • Haematocrit: 40.3 (4.7)% • Estimated glomerular filtration rate: 82.2 (14.6) ml/min/1.73 m^2 • Aortic valve Vmax, pre-AVR: 4.5 (0.8) m/s • Aortic valve mean gradient, pre-AVR: 50.4 (17.3) mmHg • Aortic valve area index, pre-AVR: 0.45 (0.13) cm^2/m^2 • Aortic valve Vmax, post-AVR: 2.4 (0.5) m/s • Aortic valve mean gradient, post-AVR: 11.6 (6.4) mmHg • Aortic valve area index, post-AVR: 1.05 (0.28) cm^2/m^2 **Population source:** those matching inclusion criteria from a single centre between 2012 and 2016. Unclear if consecutive.
Prognostic variable	LVEF <50% on pre- AVR CMR LVEF ≥50% on pre-AVR CMR (referent) Patients had CMR and echocardiography 1 month prior to AVR. CMR performed using standard protocols with LGE images and post-contrast T1 mapping acquired within 15 min following gadolinium injection. LGE-CMR images were analysed by an experienced radiologist and blinded to patient information. Region of myocardial fibrosis was defined as the sum of pixels with signal intensity >5 SDs of normal remote myocardium at each short-axis slice.
Confounders	Multivariate Cox proportional hazard regression model with backward selection analysis used for univariate markers with P-values <0.100. Factors included in adjusted analysis: atrial fibrillation, anaemia (<13 g/dL in men and <12 g/dL in women), mild renal dysfunction (eGFR <75 ml/min/1.73 m^2) and diffuse myocardial fibrosis on pre-AVR CMR.

Reference	**Hwang 2020[123] (also reported above for CMR myocardial fibrosis)**
	The prespecified confounder in the protocol (age) does not appear to have been included in the multivariate analysis.
Outcomes and effect sizes	**<u>Cardiovascular death, hospitalisation for cardiac causes, non-fatal stroke and symptomatic aggravation (worsening NYHA functional class) following AVR</u>** **Unadjusted HR 1.598 (0.567 to 4.505) for LVEF <50% vs ≥50% on pre-AVR CMR** During follow-up post-AVR, 17 patients experienced the composite endpoint, which included n=2 cardiovascular deaths, n=6 hospitalisation for cardiac causes, n=1 stroke and n=15 symptom aggravation. Patients were followed for the occurrence of the composite endpoint by February 2018 using hospital records and telephone interviews. For outcome analysis using baseline CMR parameters, the date of AVR was defined as the index date to calculate time to outcomes. Median (IQR) follow-up following AVR: 38.8 (25.8-57.6) months.
Comments	**<u>Cardiovascular death, hospitalisation for cardiac causes, non-fatal stroke and symptomatic aggravation (worsening NYHA functional class) following AVR</u>** Risk of bias: 1. Study participation LOW 2. Study attrition HIGH 3. Prognostic factor measurement LOW 4. Outcome Measurement LOW 5. Study confounding HIGH 6. Statistical analysis HIGH 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH Indirectness: • Population – all already scheduled for AVR so does not appear to be uncertainty as to whether there is an indication for intervention • Outcome – composite outcome of multiple outcomes in protocol combined rather than reported separately • Confounding – univariate only. Downgraded for this as part of risk of bias rating, so not downgraded further for indirectness.

Reference	Lindsay 2016[158]
Study type and analysis	Retrospective cohort study – unclear but appears to be a review of data that was not originally obtained for this specific study. Univariate Cox regression analysis UK
Number of participants and characteristics	N=190 (note, n=3 patients where LV function on CMR unknown) LV ejection fraction (LVEF) 30-49% on CMR, n=65 LVEF ≥50% on CMR, n=108 LVEF <30% on CMR, n=14 LVEF ≥50% on CMR, n=108 Undergoing TAVI for aortic stenosis (AS). All cases were discussed at multidisciplinary team meeting, including cardiothoracic surgeons, cardiologists and radiologists, with all available imaging being reviewed. All patients gave consent for TAVI procedure and were followed up prospectively in outpatient facility at 6 weeks, 6 months, 12 months and annually after that, unless follow-up was requested sooner by the patient. Population indirectness as all deemed to have indication for intervention already and does not represent a population where there is uncertainty about whether or not to intervene. **Inclusion criteria:** Underwent TAVI for AS; CMR completed prior to TAVI procedure. **Exclusion criteria:** Not reported. **Values listed below are presented as mean (95% CI), median (IQR) or number (%)** • Age, median (IQR): 81 (74.9-85.5) years • Male/female: 95/95 (50%/50%) • Diabetes mellitus, 142 (74.7%) • Smoking:

Reference	Lindsay 2016[158]
	- Never smoked, 102 (53.7%) - Current/ex-smoker, 88 (46.3%) • Body mass index, mean (95% CI): 26.6 (25.7-27.4) kg/m^2 • Creatinine, median (IQR): 92 (73-117) • Previous myocardial infarction, 33 (17.4%) • History of pulmonary disease, 38 (20.3%) • History of neurological disease, 36 (19%) • Extracardiac arteriopathy, 33 (17.4%) • Preoperative heart rhythm: - Sinus rhythm, 114 (60%) - Atrial fibrillation/flutter, 38 (20%) - First-degree heart block, 10 (5.3%) - Other, 28 (14.7%) • Previous cardiac surgery: - None, 137 (72.1%) - Coronary artery bypass grafting, 39 (20.5%) - Valve operation, 14 (7.4%) • Critical preoperative status, 8 (4.2%) • Previous percutaneous coronary intervention - None, 131 (68.9%) - Not part of hybrid, 52 (27.4%) - Part of hybrid, 7 (3.7%) • Canadian Cardiovascular Society: - No angina, 112 (58.9%) - No limitation of physical activity, 13 (6.8%) - Slight limitation of ordinary activity, 43 (22.6%) - Marked limitation of physical activity, 20 (10.5%) - Unknown, 2 (1.1%) • NYHA class: - No/slight limitation, 49 (25.8%) - Marked limitation of physical activity, 124 (65.3%)

Reference	Lindsay 2016[158]
	○ Symptoms at rest, 15 (7.9%) ○ Unknown, 2 (1.1%) • Extent of coronary vessel disease: ○ No vessels, 128 (67.4%) ○ 1 vessel, 27 (14.2%) ○ 2 vessels, 12 (6.3%) ○ 3 vessels, 20 (10.5%) ○ Unknown, 3 (1.6%) • Left main stem disease, 13 (6.8%) • TAVI delivery route: ○ Femoral-percutaneous, 131 (68.9%) ○ Direct aortic, 46 (24.2%) ○ Other, 10 (5.3%) ○ Unknown, 3 (1.6%) • Gadolinium on CMR: ○ Tested, 122 (64.2%) ○ Present, 78/122 (63.9%) ○ Absent, 44/122 (36.1%) • RV ejection fraction <50%, 45 (23.7%) • Peak velocity on CMR, median (IQR): 3.7 (3.5-3.9) m/s • LV ejection fraction on CMR, median (IQR): 62 (59-67)% • End-diastolic volume on CMR, median (IQR): 142 (133-153) ml • End-systolic volume on CMR, median (IQR): 48 (41-59) ml • Stroke volume on CMR, median (IQR): 86 (80-88) ml • RV end-diastolic volume on CMR, median (IQR): 124 (117-135) ml • RV stroke volume on CMR, median (IQR): 72 (67-77) ml • RV end-systolic volume on CMR, median (IQR): 50 (44-55) ml • Aortic valve area on CMR, median (IQR): 0.70 (0.70-0.74) cm^2 • Indexed aortic valve area on CMR, median (IQR): 0.41 (0.39-0.43) cm/m^2 • Indexed mass on CMR, median (IQR): 90 (84-95) g/m^2 • LV hypertrophy on CMR:

Reference	Lindsay 2016[158]
	○ Yes, 82 (30.1%) ○ No, 51 (38.6%) ○ Unknown, 57 (37.5%) • LV function: ○ ≥50%, 108 (56.8%) ○ 30-49%, 65 (34.2%) ○ <30%, 14 (7.4%) ○ Unknown, 3 (1.6%) • Pulmonary artery systolic pressure, median (IQR): 35 (33-38) mmHg • Aortic valve peak gradient on echo, median (IQR): 73 (70-76) mmHg • Aortic valve area on echo, median (IQR): 0.6 (0.6-0.7) cm^2 • Aortic annular diameter on echo, median (IQR): 23 (23-24) mm **Population source:** those matching inclusion criteria at a single hospital between 2007 and 2012. Unclear if consecutive.
Prognostic variable	LVEF 30-49% on CMR LVEF ≥50% on CMR (referent) LVEF 30-49% on CMR LVEF ≥50% on CMR (referent) Since start of TAVI program at the hospital in 2007, all patients accepted for TAVI have undergone CMR, as long as there were no contraindications to CMR (e.g. permanent pacing system), patients consented to the scan and were able to tolerate and complete the scan. CMR was performed using 1.5T scanner and standardised protocol. No mention of specific methods used to assess LVEF on CMR. ≥50% was considered to indicate good LV function, 30-49% fair LV function and <30% poor LV function.
Confounders	Univariate Cox regression analysis Multivariate models performed in the paper but not for factors LVEF status on CMR. Factors included in adjusted analysis: univariate analysis only. For operative mortality, age was prespecified as a factor that should be adjusted for and has not been included as only univariate results available for this prognostic factor.

Reference	**Lindsay 2016[158]**
Outcomes and effect sizes	**<u>All-cause mortality following TAVI</u>** <u>LVEF 30-49% vs. LVEF ≥50% on CMR</u> **HR 1.19 (95% CI 0.69 to 2.04, P=0.533) for LVEF 30-49% on CMR vs. LVEF ≥50% on CMR** <u>LVEF <30% vs. LVEF ≥50% on CMR</u> **HR 2.54 (95% CI 1.17 to 5.54, P=0.019) for LVEF 30-49% on CMR vs. LVEF ≥50% on CMR** During follow-up, 64/190 patients died. At 1 year, the number of deaths was 31. Mortality data were obtained from hospital notes and the National Strategic Tracing Service, which is a national database for all NHS patients in the UK. Median (IQR) follow-up: 850 (403-1265) days. Of surviving patients, 95.3% had at least 1 year of follow-up before the end of the study.
Comments	**<u>All-cause mortality following TAVI</u>** <u>LVEF 30-49% vs. LVEF ≥50% on CMR</u> 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 LOW 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH Indirectness: • Population – all already had indication for intervention as underwent TAVI. Therefore, does not represent population where there is uncertainty about whether there is an indication for intervention. • Prognostic factor – splits LVEF on CMR into two separate thresholds each compared with the referent, rather than comparing a single threshold (e.g. LVEF <50% vs. ≥50% or LVEF <30% vs. LVEF ≥30%). Also some uncertainty as to whether this is LVEF

Reference	Lindsay 2016[158]
	as assessed on CMR rather than echocardiography, but overall appears that it is based on CMR measurements, though not explicitly stated. • Confounding – only univariate results available for this prognostic factor and is therefore not adjusted for age which was the prespecified confounder for postoperative mortality. However, the study was included due to a lack of other available studies for this prognostic factor. Downgraded for this as part of risk of bias rating, so not downgraded further for indirectness. <u>LVEF <30% vs. LVEF ≥50% on CMR</u> 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 LOW 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH Indirectness: • Population – all already had indication for intervention as underwent TAVI. Therefore, does not represent population where there is uncertainty about whether there is an indication for intervention. • Prognostic factor – splits LVEF on CMR into two separate thresholds each compared with the referent, rather than comparing a single threshold (e.g. LVEF <50% vs. ≥50% or LVEF <30% vs. LVEF ≥30%). Also some uncertainty as to whether this is LVEF as assessed on CMR rather than echocardiography, but overall appears that it is based on CMR measurements, though not explicitly stated. • Confounding – only univariate results available for this prognostic factor and is therefore not adjusted for age which was the prespecified confounder for postoperative mortality. However, the study was included due to a lack of other available studies for this prognostic factor. Downgraded for this as part of risk of bias rating, so not downgraded further for indirectness.

D.2 Aortic stenosis – myocardial fibrosis on cardiac MRI

Reference	Agoston-Coldea 2019[6]
Study type and analysis	Prospective cohort pilot study Multivariable Cox regression model
Number of participants and characteristics	Total n=52 LGE positive: 30 LGE negative: 22 LGE distribution was mid-wall in 12 patients (23%), in the sub-epicardial myocardium in 5 patients (9.6%), was focal in 10 patients (19.2%), and diffuse in 3 patients (5.7%) **Inclusion criteria** Severe AS undergoing aortic valve replacement. Severe AS was defined as (1) peak aortic jet velocity ≥ 4 m/s, and/or (2) mean transvalvular gradient≥ 40 mmHg, and/or (3) aortic valve area (AVA) ≤ 1.0 cm^2 as assessed by echocardiography **Exclusion criteria** Contraindications for CMR (including incompatible metallic devices, significant chronic renal disease with estimated glomerular filtration rate < 30 mL/min/1.73 m^2, or claustrophobia), other significant valvular disease, rheumatic valve disease with significant (at least moderate) mitral stenosis, post-irradiation AS, history of previous myocardial infarction with or without coronary revascularization by percutaneous coronary intervention and/or bypass, previous surgery for valvular disease, active inflammatory, infectious diseases, or neoplasia, cirrhosis, pulmonary fibrosis, poor echocardiographic window or those who did not agree to participate **Values listed below are presented as mean (SD), median (IQR) or number (%)** **Patient characteristics:** Age: 66 (7.5) years Male: 55.7% Smoking: 36.5% CAD: 32.6% NYHA class ≥ III: 28.8% Logistic EuroScore II: 3.8 (1.3-5.9) Systolic blood pressure, mmHg: 132 (18.1) Chronic obstructive lung disease: 11.5%

Reference	Agoston-Coldea 2019[6]
	NT-proBNP, pg/mL: 1960 (170-9893) Preserved LVEF: 73% **Population source**: single site in Romania, between March 2016 and August 2018. Consecutive sample, but 76/128 ineligible for inclusion
Prognostic variable	**Presence or absence of LGE on CMR imaging.** Each patient underwent the same investigation protocol, including medical history, clinical examination, the recording of a 12-lead electrocardiogram, 24-h Holter monitoring, 6-min walk test, biochemical analysis, echocardiography and CMR imaging, which were all performed during the same hospital visit. All CMR imaging examinations were performed by two experienced examiners, one cardiologist and one radiologist *blinded* to all clinical data. Post-contrast, standard LGE images were acquired 10 minutes after intravenous injection of 0.2 mmol/kg gadolinium contrast agent in long- and short axis-views, using a segmented inversion-recovery gradient-echo sequence. Inversion time was adjusted to optimize nulling of apparently normal myocardium. The presence and distribution of LGE in the LV were assessed from short-axis images, using the 17-segments model, and the LGE distribution was characterised as mid-wall, subepicardial, focal or diffuse. The kappa coefficients of agreement were 0.89 (inter-reader) and 0.91 (intra-reader) for the assessment of LGE
Confounders	A stepwise multivariate Cox regression model was constructed, including age, 6MWD, E/E'ratio, LVEF, LAS and the presence of LGE
Outcomes and effect sizes	**Composite outcome:** major adverse cardiac events (MACE), including sudden cardiac death, non-fatal myocardial infarction, sustained ventricular arrhythmias, third-degree atrioventricular block and hospitalization for heart failure. 22 patients (42.3%) had MACEs: non-fatal myocardial infarction (n = 2), sustained ventricular arrhythmias (n = 2), third-degree atrioventricular block (n = 3) and hospitalization for heart failure (n = 15). In three patients, MACEs (ventricular tachycardia and hospitalization for heart failure, respectively) occurred before surgery. One patient developed third degree atrio-ventricular block during surgery and required permanent pacing. Nineteen other patients experienced MACEs after aortic valve replacement. Most patients (n = 17, 77.2%) with LGE on CMR imaging had MACEs during follow-up. Adjusted HR = 11.3 (95% CI 1.82–70.2) for LGE present vs LGE absent

Reference	Agoston-Coldea 2019[6]
	Median time interval of 386 days (interquartile range: 60 to 730 days) follow-up by completing a questionnaire either on hospital visits, telephone house-calls, or both.
Comments	Risk of bias: 1. Study participation LOW 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement LOW 5. Study confounding LOW 6. Statistical analysis HIGH 7. Other risk of bias LOW OVERALL RISK OF BIAS HIGH Indirectness: • Outcome – indirect outcome definition, a composite of events including some protocol outcomes • Population – all having aortic valve replacement, so need for intervention already determined

Reference	Barone-Rochette 2014[22]
Study type and analysis	Prospective cohort study Multivariate Cox proportional hazards model. Belgium
Number of participants and characteristics	N=154 undergoing surgical aortic valve replacement (AVR) Late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR), n=44 No LGE on CMR, n=110 Patients with severe aortic stenosis (AS) undergoing surgical AVR, with no prior myocardial infarction. Results for those receiving TAVI are also mentioned, but no multivariate results for this group are reported. Therefore, results for only the surgical AVR group were extracted.

Reference	Barone-Rochette 2014[22]
	AVR was performed with a bioprosthesis in 148 patients (96%) and with a mechanical valve in 6 patients (4%). Of these, 110 had isolated AVR while 44 patients also had coronary artery bypass grafting. Postoperative echocardiography demonstrated correct functioning of prosthesis with no patient-prosthesis mismatch. **Inclusion criteria:** >50 years of age; hospitalised for preoperative evaluation of severe degenerative AS (aortic valve area <1.0 cm^2 or <0.6 cm/m^2 by transthoracic echocardiography); undergoing AVR. **Exclusion criteria:** Prior myocardial infarction; contraindications to cardiac magnetic resonance (CMR) imaging (e.g. presence of pacemaker or defibrillator, or severe renal dysfunction defined as glomerular filtration rate <30 ml/min); co-existing severe aortic regurgitation; co-existing severe mitral or tricuspid valve disease requiring repair or replacement of these valves; undergoing other treatments for AS (e.g. Ross procedure); undergoing repeat AVR operation; prior coronary surgery; active malignancy or other conditions leading to a life expectancy <1 year discovered during workup. **Values listed below are presented as mean (SD) or number (%)** LGE on CMR • Age: 75 (9) years • Male/female: 28/16 (64%/36%) • Hypertension, 26 (59%) • Hyperlipidaemia, 25 (57%) • Smoking history: o Former smoker, 9 (21%) o Current smoker, 7 (16%) • Diabetes, 15 (34%) • Family history of coronary artery disease, 9 (20%) • NYHA functional class III/IV, 13 (30%) • Chest pain, 9 (21%) • Syncope, 5 (11%) • Chronic obstructive pulmonary disease, 8 (18%) • Peripheral artery disease, 5 (11%)

Reference	Barone-Rochette 2014[22]
	- Stroke, 6 (14%) - Prior percutaneous coronary intervention, 2 (5%) - Glomerular filtration rate: 72 (25) ml/min/m^2 - Logistic EuroSCORE I: 7.6 (4.9)% - STS score: 2.5 (1.4)% - Atrial fibrillation, 5 (9%) - Left bundle branch block, 6 (14%) - Systolic blood pressure: 135 (20) mmHg - Heart rate: 69 (13) bpm - Aortic valve area: 0.70 (0.18) cm^2 - Indexed aortic valve area: 0.38 (0.09) cm^2/m^2 - Peak transvalvular aortic gradient: 77 (28) mmHg - Mean transvalvular aortic gradient: 47 (18) mmHg - Coronary artery disease, 12 (29%) - Vessels affected by coronary disease: 1.9 (1.2) - Indexed end-diastolic volume on CMR: 83 (27) ml/m^2 - Indexed end-systolic volume on CMR: 41 (28) ml/m^2 - Ejection fraction on CMR: 55 (18)% - Indexed LV mass: 99 (31) g/m^2 No LGE on CMR - Age: 74 (9) years - Male/female: 68/142 (62%/38%) - Hypertension, 70 (64%) - Hyperlipidaemia, 70 (64%) - Smoking history: ○ Former smoker, 31 (28%) ○ Current smoker, 16 (12%)

Reference	**Barone-Rochette 2014**[22]
	- Diabetes, 20 (18%) - Family history of coronary artery disease, 22 (20%) - NYHA functional class III/IV, 29 (26%) - Chest pain, 22 (20%) - Syncope, 6 (5%) - Chronic obstructive pulmonary disease, 10 (9%) - Peripheral artery disease, 11 (10%) - Stroke, 9 (8%) - Prior percutaneous coronary intervention, 3 (3%) - Glomerular filtration rate: 75 (30) ml/min/m^2 - Logistic EuroSCORE I: 7.0 (5.7)% - STS score: 2.2 (1.5)% - Atrial fibrillation, 10 (9%) - Left bundle branch block, 8 (7%) - Systolic blood pressure: 134 (21) mmHg - Heart rate: 70 (15) bpm - Aortic valve area: 0.71 (0.16) cm^2 - Indexed aortic valve area: 0.38 (0.08) cm^2/m^2 - Peak transvalvular aortic gradient: 80 (25) mmHg - Mean transvalvular aortic gradient: 49 (16) mmHg - Coronary artery disease, 31 (28%) - Vessels affected by coronary disease: 1.6 (0.7) - Indexed end-diastolic volume on CMR: 79 (24) ml/m^2 - Indexed end-systolic volume on CMR: 33 (23) ml/m^2 - Ejection fraction on CMR: 61 (14)% - Indexed LV mass: 93 (22) g/m^2 <u>LGE on CMR</u>

Reference	Barone-Rochette 2014[22]

	• Age: 75 (9) years
	• Male/female: 28/16 (64%/36%)
	• Hypertension, 26 (59%)
	• Hyperlipidaemia, 25 (57%)
	• Smoking history:
	  ○ Former smoker, 9 (21%)
	  ○ Current smoker, 7 (16%)
	• Diabetes, 15 (34%)
	• Family history of coronary artery disease, 9 (20%)
	• NYHA functional class III/IV, 13 (30%)
	• Chest pain, 9 (21%)
	• Syncope, 5 (11%)
	• Chronic obstructive pulmonary disease, 8 (18%)
	• Peripheral artery disease, 5 (11%)
	• Stroke, 6 (14%)
	• Prior percutaneous coronary intervention, 2 (5%)
	• Glomerular filtration rate: 72 (25) ml/min/m^2
	• Logistic EuroSCORE I: 7.6 (4.9)%
	• STS score: 2.5 (1.4)%
	• Atrial fibrillation, 5 (9%)
	• Left bundle branch block, 6 (14%)
	• Systolic blood pressure: 135 (20) mmHg
	• Heart rate: 69 (13) bpm
	
	• Aortic valve area: 0.70 (0.18) cm^2
	• Indexed aortic valve area: 0.38 (0.09) cm^2/m^2
	• Peak transvalvular aortic gradient: 77 (28) mmHg
	• Mean transvalvular aortic gradient: 47 (18) mmHg
	• Coronary artery disease, 12 (29%)
	• Vessels affected by coronary disease: 1.9 (1.2)

Reference	**Barone-Rochette 2014**[22]
	- Indexed end-diastolic volume on CMR: 83 (27) ml/m^2 - Indexed end-systolic volume on CMR: 41 (28) ml/m^2 - Ejection fraction on CMR: 55 (18)% - Indexed LV mass: 99 (31) g/m^2 **Population source:** patients matching inclusion criteria from a single institution in Belgium between February 2005 and November 2012.
Prognostic variable	LGE on CMR No LGE on CMR (referent) CMR performed with 10-12 consecutive short-axis images covering entire left ventricle. Single 2-, 3- and 4-chamber long-axis images were obtained using cine steady-state free-precession sequence to assess myocardial function and mass. At 10-15 min following gadolinium-based contrast agent injection, identical prescriptions of short- and long-axis slices were obtained using 2D or 3D inversion recovery sequence to allow LGE to be assessed. LGE was quantified using a fully automated method and results were expressed as a percentage of the myocardial mass. Mean (SD) of signal intensity in 5 sectors per slice calculated using this method. Region with lowest signal intensity is considered ‘remote’ myocardium and LGE regions are considered >2.4 SD of remote. The pattern of LGE was assessed by two independent observers who were blinded to clinical data, coronary anatomy and outcomes. Discordant findings were resolved by consensus. A total of 44 patients had significant LGE (>1%), with the mean percentage of myocardium affected by LGE being 3.5 (2.3)% in these patients. Of these 44 patients, 14 had infarct LGE, 20 had focal LGE, 7 had diffuse LGE and 3 had septal stripe LGE. CMR performed at median of 3 days (range, 0-180 days) prior to surgery.
Confounders	Multivariate Cox proportional hazards model. All clinical parameters were considered for inclusion in the univariate Cox proportional hazards model and all of those with significant univariate correlates of survival were entered into the forward stepwise multivariate Cox model. Factors included in adjusted analysis: presence of LGE, NYHA functional class III/IV and left bundle branch block – assumed that only these three were included in the multivariate analysis as they were only significant ones on univariate analysis. Age does not appear to have been included in the multivariate model, which was the confounding factor prespecified in the protocol for this outcome. Age is however similar between the LGE and no LGE groups.

Reference	Barone-Rochette 2014[22]
Outcomes and effect sizes	**<u>All-cause mortality following surgical AVR</u>** **HR 2.80 (95% CI 1.10 to 6.90, P=0.025) for LGE on CMR vs. no LGE on CMR** Survival status was obtained by phone contact with patients, relative or their physician. Patient history and treatment were obtained from medical files and from review of visit or hospital records. Cause of death was classified as cardiac or non-cardiac. Cardiovascular mortality was defined as due to congestive heart failure, myocardial infarction, sudden death or occurring after an AVR procedure. During follow-up after surgical AVR, there were 21 deaths (n=11 cardiovascular-related). Of these, 5 were postoperative deaths occurring within 30 days of AVR or during hospitalisation (3 sudden deaths, 1 postoperative heart failure and 1 perioperative stroke). Of the 11 cardiovascular-related deaths, 6 occurred after 30 days (3 sudden deaths, 1 due to heart failure, 1 due to infective endocarditis and 1 due to aneurysm rupture). The 10 non-cardiac deaths were due to cancer (n=7), sepsis (n=1), cerebral haemorrhage following a fall (n=1) and suicide (n=1). No multivariate results were available for cardiovascular-related deaths or postoperative deaths within 30 days. Median follow-up: 2.9 years (100% complete) in those receiving surgical AVR.
Comments	**<u>All-cause mortality following surgical AVR</u>** Risk of bias: 1. Study participation LOW 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement LOW 5. Study confounding HIGH 6. Statistical analysis VERY HIGH 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH Indirectness: • Population - all already scheduled to have AVR so population is not those where there is uncertainty about whether or not intervention is indicated • Confounding – the confounder prespecified in the protocol for this outcome (age) does not appear to have been adjusted for in the multivariate analysis. Downgraded for this as part of risk of bias rating, so not downgraded further for indirectness.

Reference	Christensen 2017[57]
Study type and analysis	Prospective cohort study Multivariate Cox proportional hazards analysis Denmark
Number of participants and characteristics	N=78 (n=92 overall with cardiac MRI performed, but only n=78 had data for fibrosis) Fibrosis on cardiac MRI, n=21 No fibrosis on cardiac MRI, n=57 Asymptomatic severe aortic stenosis (AS). Judged asymptomatic prior to enrolment by experienced cardiologist not taking part in the study and this was confirmed by study staff at time of inclusion. **Inclusion criteria:** ≥18 years old; severe asymptomatic AS (aortic valve area <1.0 cm^2 and maximal aortic peak velocity >3.5 m/s); LV ejection fraction (LVEF) >50%; cardiac MRI performed. **Exclusion criteria:** Chronic kidney disease (p-creatinine ≥200 μmol/L); permanent ventricular pacing; chronic atrial fibrillation; inability to perform exercise testing; co-existent >mild mitral valve disease or aortic insufficiency. **Values listed below are presented as mean (SD) or number (%)** Whole cohort of 92 patients – not limited to the 78 with data available for fibrosis on cardiac MRI • Age: 74 (8) years • Male/female: 52/40 (57%/43%) • Coronary artery disease, 3 (3%) • Hypertension, 63 (68%) • Peripheral artery disease, 1 (1%) • Diabetes mellitus, 12 (13%) • Diuretics, 29 (32%)

Reference	**Christensen 2017[57]**
	- Beta-blockers, 13 (14%) - Calcium channel blockers, 26 (28%) - Angiotensin inhibitors, 41 (45%) - Statins, 43 (47%) - Estimated glomerular filtration rate: 75 (17) ml/min - Left atrial volume index: 36 (8) ml/m^2 - Relative wall thickness: 0.47 (0.08) - LV mass: 186 (39) g - LV mass index: 100 (19) g/m^2 - Aortic valve area: 0.83 (0.15) cm^2 - Aortic valve area index: 0.45 (0.08) cm^2/m^2 - Vmax: 4.20 (0.57) - Mean gradient: 45 (14) mmHg - E-velocity: 0.77 (0.22) m/s - A-velocity: 1.03 (0.30) m/s - Deceleration time: 294 (93) msec - E/e’ medial: 13 (5) - Diastolic function: 22/49/21/10 - Peak atrial longitudinal strain: 26 (6)% - Tricuspid annular plane systolic excursion: 24 (3) mm - S’ right ventricle: 13 (2) cm/s - Brain natriuretic peptide, median (IQR): 51 (29-70) pg/ml - LV end-diastolic volume index on cardiac MRI: 80 (17) ml/m^2 - LV end-systolic volume index on cardiac MRI: 31 (10) ml/m^2 - LV ejection fraction on cardiac MRI: 62 (7)% - Right atrial volume index on cardiac MRI: 50 (12) ml/m^2 - Right atrial emptying fraction on cardiac MRI: 42 (9)% - RV end-diastolic volume index on cardiac MRI: 66 (14) ml/m^2

Reference	Christensen 2017[57]
	- RV end-systolic volume index on cardiac MRI: 26 (7) ml/m^2 - RV ejection fraction on cardiac MRI: 62 (7)% - LV mass on cardiac MRI: 130 (36) g - LV mass index on cardiac MRI: 69 (17) g/m^2 - Aortic stroke volume on cardiac MRI: 70 (18) ml - Aortic stroke volume index on cardiac MRI: 38 (8) ml/m^2 - Aortic regurgitant fraction on cardiac MRI: 8 (6)% - Fibrosis on cardiac MRI on cardiac MRI: 21/78 (27%) **Population source:** appear to be patients matching inclusion criteria at a single centre, though is unclear. Dates of recruitment not specified. Unclear if consecutive.
Prognostic variable	Fibrosis on cardiac MRI No fibrosis on cardiac MRI (referent) Cardiac MRI obtained sequential short-axis slices enclosing entire heart during multiple breath hold sequences acquiring slices of 8 mm thickness. Delayed enhancement imaging performed 10-15 min following administration of gadoterate meglumine. Optimal inversion time, to null the myocardium, was determined using Look-Locker sequence with multiple images with varying inversion time. Images were analysed blinded for clinical and echocardiographic data by an experienced examiner using software. Late gadolinium enhancement was performed in 78 of the 92 enrolled patients, with 15 having midwall fibrosis, 3 having ischaemic fibrosis and 3 having nonspecific fibrosis.
Confounders	Multivariate Cox proportional hazards analysis Factors included in adjusted analysis: age, gender and aortic mean gradient One of the pre-specified confounders included in analysis (age), but not the other (smoking).
Outcomes and effect sizes	**<u>Unplanned hospital admissions (for atrial fibrillation, heart failure or acute coronary syndrome), aortic valve replacement (AVR) or death</u>** **HR 1.17 (95% CI 0.44 to 3.11) for fibrosis on cardiac MRI vs. no fibrosis on cardiac MRI** For the whole cohort of 92 patients, 28 events occurred (n=22 referred for AVR due to symptoms developing, n=4 deaths and n=2 unplanned hospitalisations). Note that data was not provided for the subset of 78 patients that had the presence or absence of fibrosis assessed on cardiac MRI.

Reference	**Christensen 2017**[57]
	Decision to perform AVR was made by a heart team not participating in the study according to guidelines. Follow-up for the composite end-point was by review of electronic hospital records and Danish Civil registration system, where all deaths in Denmark are registered within 2 weeks. Follow-up was completed in August 2016. Median follow-up: 358 days (note this was for the whole cohort of 92 patients and not limited to the 72 included in fibrosis analysis).
Comments	**Unplanned hospital admissions (for atrial fibrillation, heart failure or acute coronary syndrome), AVR or death** Risk of bias: 1. Study participation HIGH 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement HIGH 5. Study confounding HIGH 6. Statistical analysis HIGH 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH Indirectness: • Outcome – composite outcome of three separate outcomes listed in the protocol, rather than reporting them separately. • Confounding – though adjustment for one of the confounders pre-specified in the protocol has been performed (age) as well as other factors, the other pre-specified confounder for this outcome (smoking) was not included. Downgraded for this as part of risk of bias rating, so not downgraded further for indirectness.

Reference	**Dweck 2011**[84]
Study type and analysis	Prospective cohort study Multivariate Cox proportional hazards regression UK
Number of participants	N=143

Reference	**Dweck 2011[84]**
and characteristics	Midwall fibrosis based on late gadolinium enhancement (LGE) pattern on cardiac magnetic resonance (CMR), n=54 No LGE on CMR, n=49 Infarct pattern fibrosis based on LGE on CMR, n=40 No LGE on CMR, n=49 Moderate or severe aortic stenosis (AS) receiving CMR. At the institution, local guidelines recommend CMR for all of those with severe AS. Other reasons for referral included diagnostic evaluation, clarification of disease severity, preoperative evaluation and assessment of hypertrophic response. In the whole cohort, aortic valve replacement (AVR) was performed during follow-up in 50%, with no difference in rates among the three groups. Population indirectness as some may already have had indication for intervention prior to CMR being performed. **Inclusion criteria:** Underwent CMR with gadolinium injection; moderate or severe AS (peak aortic valve pressure gradient >36 mmHg and peak transvalvular velocity >3 m/s on Doppler echocardiography); **Exclusion criteria:** Disseminated malignancy; moderate or severe aortic regurgitation, mitral regurgitation or mitral stenosis; contraindications to CMR, including pacemaker and defibrillator implantation; estimated glomerular filtration rate <30 ml/min. **Values listed below are presented as mean (SD) or number (%)** <u>Midwall LGE</u> • Age: 70 (11) years • Male/female: 39/15 (72%/28%) • Atrial fibrillation, 10 (18%) • Diabetes mellitus, 10 (19%) • Hypertension, 28 (55%) • Bicuspid aortic valve, 9 (17%) • Documented coronary artery disease, 23 (42%) o 1-vessel, 9 (17%) o 2-vessel, 3 (6%)

Reference	**Dweck 2011**[84]
	- 3-vessel, 7 (13%) - Previous percutaneous coronary intervention, 5 (9%) - Previous coronary artery bypass grafting, 4 (8%) - ACE inhibitor, 26 (48%) - Beta-blocker, 14 (26%) - Statins, 32 (60%) - Diuretic use, 19 (36%) - Aortic valve area on CMR: 1.00 (0.31) cm^2 - Peak aortic valve gradient by echocardiography: 70 (26) mmHg - Severe AS, 27 (50%) - Ejection fraction: 58 (21)% - Indexed left atrial volume, geometric mean (95% CI): 62.9 (56.2-70.3) ml/m^2 - Indexed left ventricular end-diastolic volume, geometric mean (95% CI): 88.5 (79.4-98.6) ml/m^2 - Indexed left ventricular mass, geometric mean (95% CI): 113.7 (104.5-123.8) g/m^2 - Right ventricular ejection fraction: 57 (12)% - % LGE mass: 5.2 Infarct LGE - Age: 70 (13) years - Male/female: 32/8 (80%/20%) - Atrial fibrillation, 7 (18%) - Diabetes mellitus, 13 (32%) - Hypertension, 20 (50%) - Bicuspid aortic valve, 9 (23%) - Documented coronary artery disease, 39 (98%) - 1-vessel, 6 (15%) - 2-vessel, 8 (20%) - 3-vessel, 11 (28%) - Previous percutaneous coronary intervention, 12 (30%) - Previous coronary artery bypass grafting, 11 (28%)

Reference	Dweck 2011[84]

	• ACE inhibitor, 24 (61%)
	• Beta-blocker, 20 (49%)
	• Statins, 33 (82%)
	• Diuretic use, 16 (41%)
	• Aortic valve area on CMR: 0.91 (0.26) cm^2
	• Peak aortic valve gradient by echocardiography: 69 (16) mmHg
	• Severe AS, 26 (65%)
	• Ejection fraction: 44 (18)%
	• Indexed left atrial volume, geometric mean (95% CI): 63.3 (57.1-70.2) ml/m^2
	• Indexed left ventricular end-diastolic volume, geometric mean (95% CI): 101.4 (92.6-111.0) ml/m^2
	• Indexed left ventricular mass, geometric mean (95% CI): 97.8 (90.9-105.2) g/m^2
	• Right ventricular ejection fraction: 55 (14)%
	• % LGE mass: 7.3
	
	No LGE
	• Age: 64 (16) years
	• Male/female: 26/23 (53%/47%)
	• Atrial fibrillation, 10 (21%)
	• Diabetes mellitus, 12 (25%)
	• Hypertension, 27 (56%)
	• Bicuspid aortic valve, 14 (29%)
	• Documented coronary artery disease, 18 (37%)
	  ○ 1-vessel, 8 (16%)
	  ○ 2-vessel, 1 (2%)
	  ○ 3-vessel, 1 (2%)
	  ○ Previous percutaneous coronary intervention, 5 (10%)
	  ○ Previous coronary artery bypass grafting, 10 (20%)
	• ACE inhibitor, 27 (56%)
	• Beta-blocker, 27 (56%)
	• Statins, 33 (67%)

Reference	Dweck 2011[84]
	- Diuretic use, 7 (15%) - Aortic valve area on CMR: 1.05 (0.37) cm^2 - Peak aortic valve gradient by echocardiography: 70 (26) mmHg - Severe AS, 26 (53%) - Ejection fraction: 69 (13)% - Indexed left atrial volume, geometric mean (95% CI): 58.9 (53.4-64.9) ml/m^2 - Indexed left ventricular end-diastolic volume, geometric mean (95% CI): 78.8 (72.1-86.2) ml/m^2 - Indexed left ventricular mass, geometric mean (95% CI): 92.6 (86.0-99.6) g/m^2 - Right ventricular ejection fraction: 58 (13)% - % LGE mass: 0 **Population source:** consecutive patients matching inclusion criteria at a single centre between January 2003 and October 2008.
Prognostic variable	Midwall fibrosis based on LGE pattern on CMR No LGE on CMR (referent) Infarct pattern fibrosis based on LGE on CMR No LGE on CMR (referent) CMR performed using standardised protocol. At 10-15 min following injection of gadolinium agent, inversion recovery-prepared spoiled gradient echo images were acquired in long- and short-axis views to detect areas of LGE as previously described. Inversion times were optimised to null normal myocardium images with images repeated in two separate phase-encoding directions to exclude artefact. The presence and pattern of LGE were assessed by two independent observers blinded to clinical data, including valve severity, coronary anatomy and outcomes. A third blinded observer adjudicated when there was disagreement between the first two observers. Patients with a mixed pattern of LGE were categorised according to the predominant fibrosis pattern. LGE was calculated semi-automatically by a single operator using software. Three patterns of LGE were observed: no LGE group, localised enhancement consistent with prior myocardial infarction (infarct LGE group) and a midwall pattern of LGE (midwall LGE group).
Confounders	Multivariate Cox proportional hazards regression Factors included in adjusted analysis: full list unclear, but if those included in multivariate table were all included then the factors were ejection fraction, indexed LV end-diastolic volume, midwall LGE, infarct LGE and subsequent AVR.

Reference	**Dweck 2011[84]**
	Age and smoking, which were prespecified confounders for this outcome in the protocol, do not appear to have been included in the multivariate model, though factors included in the model are unclear.
Outcomes and effect sizes	**All-cause mortality – mixture of medical and surgically treated patients (AVR possibly adjusted for in model)** **HR 5.35 (95% CI 1.16 to 24.56) for midwall LGE on CMR vs. no LGE on CMR** **All-cause mortality – mixture of medical and surgically treated patients (AVR possibly adjusted for in model)** **HR 2.56 (95% CI 0.48 to 13.64) for infarct LGE on CMR vs. no LGE on CMR** Overall, 27 patients died during follow-up: n=2 in the no LGE group, n=16 in the midwall LGE group and n=9 in the infarct LGE group. Of these, 2/2 deaths in the no LGE group, 13/16 deaths in the midwall LGE group and 8/9 deaths in the infarct LGE group were cardiac deaths. During follow-up, 72 patients (50%) had AVR (8% percutaneously), with no difference in the rate among the three groups. No multivariate results were reported for cardiac mortality. Mortality data were obtained from hospital notes and National Strategic Tracing Service, which is a national database covering all NHS patients in the UK. Cause of death was obtained from medical notes and/or death certification records and an assessment made as to whether this represented sudden cardiac death. Mean (SD) follow-up: 2.0 (1.4) years. Median follow-up was 1.7 years. No patients were lost to follow-up.
Comments	**All-cause mortality – mixture of medical and surgically treated patients (AVR possibly adjusted for in model)** Midwall LGE vs. no LGE Risk of bias: 1. Study participation LOW 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement LOW 5. Study confounding HIGH 6. Statistical analysis VERY HIGH 7. Other risk of bias LOW

Reference	Dweck 2011[84]
	OVERALL RISK OF BIAS VERY HIGH Indirectness: • Population – includes some that underwent AVR during follow-up and may have already been scheduled to undergo operation prior to CMR. Some within population may those where there is no uncertainty about whether or not intervention is indicated • Prognostic factor – provides results separately for two different types of LGE on CMR, rather than as one combined result. • Outcome – includes those with and without surgery during follow-up, whereas ideally aimed to look at results for non-operative and postoperative mortality separately • Confounding – the confounders prespecified in the protocol for this outcome (age and smoking) do not appear to have been adjusted for in the multivariate analysis. Downgraded for this as part of risk of bias rating, so not downgraded further for indirectness. Infarct LGE vs. no LGE Risk of bias: 1. Study participation LOW 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement LOW 5. Study confounding HIGH 6. Statistical analysis VERY HIGH 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH Indirectness: • Population – includes some that underwent AVR during follow-up and may have already been scheduled to undergo operation prior to CMR. Some within population may those where there is no uncertainty about whether or not intervention is indicated • Prognostic factor – provides results separately for two different types of LGE on CMR, rather than as one combined result. • Outcome – includes those with and without surgery during follow-up, whereas ideally aimed to look at results for non-operative and postoperative mortality separately • Confounding – the confounders prespecified in the protocol for this outcome (age and smoking) do not appear to have been adjusted for in the multivariate analysis. Downgraded for this as part of risk of bias rating, so not downgraded further for indirectness.

Reference	Everett 2020[88]
Study type and analysis	Data from multiple prospective cohort studies combined Multivariate Cox regression model UK, Germany, USA, Canada and South Korea
Number of participants and characteristics	N=440 Late gadolinium enhancement (LGE) on CMR, n=220 No LGE on CMR, n=220 Severe aortic stenosis (AS) scheduled for aortic valve intervention. Population indirectness as considered to be an indication for intervention in all patients already, prior to cardiac magnetic resonance (CMR) imaging. Aortic valve intervention was performed at a median of 15 (IQR, 4-58) days following CMR. This was isolated surgical aortic valve replacement (AVR) in n=311 (71%), combined coronary artery bypass grafting with surgical AVR in n=62 (14%) and transcatheter AVR in n=67 (15%). **Inclusion criteria:** Severe AS scheduled for aortic valve intervention. **Exclusion criteria:** Presence of an implantable cardiac device; advanced renal dysfunction (estimated glomerular filtration rate <30 ml/min/1.73 m^2; previous valve replacement; presence of another co-existent myocardial pathology (e.g. cardiac amyloidosis, hypertrophic cardiomyopathy or myocarditis); unable to analyse T1 maps. **Values listed below are presented as mean (SD) or number (%)** • Age: 69.67 (10.11) years • Male/female: 259/181 (59%/41%) • Body mass index: 27.60 (5.06) kg/m^2 • Body surface area: 1.85 (0.24) m^2 • Hypertension, 280 (64%)

Reference	Everett 2020[88]
	- Diabetes mellitus, 93 (21%) - Atrial fibrillation, 56 (13%) - Previous myocardial infarction, 38 (9%) - Coronary artery disease, 168 (38%) - NYHA functional class III/IV, 157 (36%) - Systolic blood pressure: 130.7 (19.84) mmHg - Diastolic blood pressure: 72.67 (12.04) mmHg - STS-PROM score, median (IQR): 1.44 (0.88-2.29)%, 1.40 (0.92-2.15)% and 1.89 (1.13-3.31)% in tertiles of extracellular volume fraction <25.9%, 25.9%-29.1% and >29.1%, respectively. - EuroSCORE II, median (IQR): 1.24 (0.82-2.19)%, 1.44 (0.99-2.21)% and 2.18 (1.14-4.28)% in tertiles of extracellular volume fraction <25.9%, 25.9%-29.1% and >29.1%, respectively. - Peak aortic jet velocity: 4.46 (0.80) m/s - Peak aortic valve gradient: 81.99 (29.68) mmHg - Mean aortic valve gradient: 49.66 (18.82) mmHg - Aortic valve area: 0.73 (0.25) cm^2 - Indexed aortic valve area: 0.40 (0.13) cm^2/m^2 - Valvuloarterial impedance: 3.92 (1.12) $mmHg/ml/m^2$ - Bicuspid aortic valve, 144 (33%) - Indexed LV end-diastolic volume: 78.33 (28.30) ml/m^2 - Indexed LV end-systolic volume, median (IQR): 17 (11-28) ml/m^2, 21 (14-36) ml/m^2 and 30 (17-51) ml/m^2 in tertiles of extracellular volume fraction <25.9%, 25.9%-29.1% and >29.1%, respectively. - Indexed LV stroke volume: 49 (13.49) ml/m^2 - LV ejection fraction: 66 (16.37)% - LV ejection fraction <50%, 71 (16%) - LV mass index: 93.33 (32.31) g/m^2 - Indexed RV end-diastolic volume: 65 (18.13) ml/m^2 - Indexed RV end-systolic volume, median (IQR): 21 (16-27) ml/m^2, 21 (15-29) ml/m^2 and 23 (16-30) ml/m^2 in tertiles of extracellular volume fraction <25.9%, 25.9%-29.1% and >29.1%, respectively. - Indexed RV stroke volume: 41.33 (10.69) ml/m^2

Reference	Everett 2020[88]
	- RV ejection fraction: 64 (10.9)% - Indexed left atrial volume: 53.33 (23.1) ml/m^2 - LGE, 220 (50%) **Population source:** patients matching inclusion criteria from multiple prospective observational cohorts (10 centres across Europe, North America and Asia).
Prognostic variable	LGE on CMR No LGE on CMR (referent) All underwent CMR with T1 mapping performed prior to and following intravenous gadolinium contrast administration. Range of different scanners used across centres. Different T1 mapping pulse sequences and field strengths were also used. Standard long-axis cine images were obtained as well as a short-axis cine stack of the left ventricle. LGE imaging with short axis left ventricle stack and standard long-axis views performed 5-15 min after gadolinium was administered. T1 mapping data acquired in short-axis mid-ventricular view of left ventricle before and 10-20 min following gadolinium administration. CMR image analysis performed by two operators within a core lab according to standardised protocol. Operators were blinded to outcome data. Presence of midwall and infarct patterns of LGE recorded and quantitative analysis performed using full-width-at-half-maximum technique. Extent of LGE expressed as percentage of total LV mass. Areas of signal contamination by epicardial fat or blood pool were manually excluded. LVEF was calculated by contouring the short-axis stack
Confounders	Multivariate Cox regression model. Variables with a significant association on univariate analysis were included in the multivariate model. Factors included in adjusted analysis: extracellular volume percentage, age, gender, LV ejection fraction <50%, LGE on CMR and peak aortic jet velocity. Though two models with different variables included were reported, the results from the model with the highest number of factors included were extracted. The only difference between the two models was the inclusion of peak aortic jet velocity in the model that has been extracted, which was not included in the other reported model. Age was the confounder prespecified in the protocol for this outcome and has been included in the multivariate model.
Outcomes and effect sizes	**<u>All-cause mortality following aortic valve intervention</u>** **HR 1.233 (95% CI 0.663 to 2.293) for LGE on CMR vs. no LGE on CMR** During follow-up, 52 deaths occurred. Of these, 7 occurred within 30 days of valve intervention (1 perioperative death). Robust cause of death data was available in 37 cases (71%) and 14 of these (38%) were considered to be cardiovascular deaths.

Reference	**Everett 2020**[88]
	The primary outcome was all-cause mortality. Cardiovascular mortality was defined as death due to myocardial ischaemic or infarction, heart failure, cardiac arrest (due to arrhythmia or unknown cause) or cerebrovascular accident. Outcome events were adjudicated by review of patient health records (including U.K. Spine database) and cause of death was adjudicated by three observers. For centres in the UK, death certificates were available for all patients. Deaths occurring at international sites outside of the UK were adjudicated using a combination of medical record review, reports from family members and death certificates. No multivariate results were provided for cardiovascular mortality. Median (IQR) follow-up: 3.8 (2.8-4.6) years. Final status checks were performed between January and August 2018 and no patient was lost to follow-up.
Comments	**<u>All-cause mortality following aortic valve intervention</u>** <u>LGE vs. no LGE on CMR</u> Risk of bias: 1. Study participation LOW 2. Study attrition LOW 3. Prognostic factor measurement HIGH 4. Outcome Measurement LOW 5. Study confounding LOW 6. Statistical analysis HIGH 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH Indirectness: • Population – all already scheduled for aortic valve intervention so no uncertainty about whether there is indication for intervention.

Reference	**Herrmann 2018**[118]
Study type and analysis	Prospective cohort study

Reference	Herrmann 2018[118]
	Multivariate Cox proportional hazards regression Germany
Number of participants and characteristics	N=58 (only 46 had data for CMR fibrosis at baseline) Mild fibrosis on cardiac magnetic resonance (CMR) imaging, n= not reported No fibrosis on CMR, n= not reported Severe fibrosis on CMR, n= not reported No fibrosis on CMR, n= not reported Symptomatic severe aortic stenosis (AS) referred to a hospital for left-sided heart catheterisation and evaluation prior to aortic valve replacement (AVR). Population indirectness as all already had an indication for intervention and underwent AVR. **Inclusion criteria:** Isolated symptomatic severe AS (symptoms one exertion and aortic valve area <1.0 cm^2). **Exclusion criteria:** Prior myocardial infarction; significant coronary artery disease (degree of stenosis >50%); prior heart surgery; malignant cancer; other valvulopathies > stage I. **Values listed below are presented as mean (SD) or number (%)** • Age: 68.3 (8.2) years • Male/female: 35/23 (60.3%/39.7%) • Body mass index: 28.9 (4.0) kg/m^2 • Systolic blood pressure: 125.4 (19.1) mmHg • Diastolic blood pressure: 74.8 (10.7) mmHg • NYHA functional class: ○ II, 8 (13.8%) ○ III, 38 (65.5%) ○ IV, 12 (20.7%)

Reference	Herrmann 2018[118]
	• Angina, 26 (44.8%) • Syncope, 8 (13.8%) • Atrial fibrillation, 13 (22.4%) • History of hypertension, 51 (87.9%) • Diabetes mellitus, 16 (27.6%) • Hyperlipoproteinaemia, 32 (55.2%) • Current smoking, 15 (25.9%) • EuroSCORE for AS: 14.9 (18.2)% • Haemoglobin: 13.4 (2.1) mg/dL • Creatinine: 1.1 (0.7) mg/dL • LV systolic pressure: 191.9 (21.5) mmHg • Stroke volume: 70.5 (21.0) ml • Peak to peak gradient: 54.5 (16.4) mmHg • Mean gradient: 45.6 (11.4) mmHg • Ejection fraction: 54.4 (10.9)% • LV end-systolic diameter: 33.8 (7.5) mm • Aortic valve area: 0.8 (0.2) cm^2 • Mean aortic gradient: 50.2 (15.6) mmHg • Maximum aortic gradient: 78.5 (22.6) mmHg • Systolic pulmonary artery pressure: 35.2 (11.5) mmHg • LV end-diastolic diameter: 50.5 (8.2) mm • Left atrial size: 40.5 (7.4) mm • Interventricular wall thickness, end-diastolic: 13.6 (2.1) mm • Posterior wall thickness, end-diastolic: 13.4 (1.5) mm • LV mass: 182.5 (61.4) g • Ejection fraction on CMR: 55.7 (10.6)% • LV end-systolic diameter on CMR: 80.5 (50.8) mm • LV end-diastolic diameter on CMR: 162.2 (64.4) mm

Reference	Herrmann 2018[118]
	- LV mass on CMR: 194.1 (64.9) g **Population source:** consecutive patients matching inclusion criteria from a single hospital between March 2006 and February 2007.
Prognostic variable	Mild fibrosis on CMR No fibrosis on CMR (referent) Severe fibrosis on CMR No fibrosis on CMR (referent) CMR was performed to assess the presence of replacement fibrosis within three days of heart catheterisation. Within three weeks, AVR was performed and two endomyocardial biopsies were taken intraoperatively from the endocardium of the basal LV septum for assessment of replacement fibrosis. CMR was performed in all patients with no contraindications. At baseline this included 46 of the 58 included in the study and it was unclear how those without data were incorporated into the prognostic analysis for this factor. For detection of fibrosis, phase-sensitive inversion recovery images were obtained 12-15 min following gadopentetate dimeglumine. Stack of multiple short-axis views covering whole LV was applied to identify changes in tissue integrity of the LV myocardium. Quantification of myocardial replacement fibrosis was performed for all LV segments and semiautomatic estimation of enhanced fibrotic areas was performed using 3 SDs above the mean value of normal myocardium. CMR was performed blinded to NYHA functional class and the amount of fibrosis assessed by myocardial biopsy. Definition of mild fibrosis on CMR appears to be the presence of 1 LGE+ segment and severe fibrosis the presence of >1 LGE+ segment, with no fibrosis being defined as the absence of any LGE+ segments, though this is interpreted from a figure within the paper rather than being explicitly explained.
Confounders	Multivariate Cox proportional hazards regression. Parameters differing between those surviving and those deceased at a level of P<0.05 were entered into univariate Cox regression analyses and were adjusted. Factors included in adjusted analysis: - Model 1: age, sex and CMR fibrosis grading - Model 2: EuroSCORE and CMR fibrosis grading Two different adjusted models were reported. Both were extracted as they contain different variables. Age was only prespecified confounder for operative mortality and has been included in the multivariate analyses. Age is one of the factors captured by EuroSCORE grading so has also been captured in the model that only adjusted for this variable.

Reference	**Herrmann 2018**[118]
Outcomes and effect sizes	**All-cause mortality following AVR** Mild fibrosis vs. no fibrosis on CMR • **Model 1 – HR 2.52 (95% CI 0.60 to 10.66, P=0.208) for mild fibrosis on CMR vs. no fibrosis on CMR** – adjusted for age and sex • **Model 2 – HR 2.98 (95% CI 0.74 to 11.96, P=0.12) for mild fibrosis on CMR vs. no fibrosis on CMR** – adjusted for EuroSCORE Severe fibrosis vs. no fibrosis on CMR • **Model 1 – HR 6.03 (95% CI 1.66 to 21.91, P=0.006) for severe fibrosis on CMR vs. no fibrosis on CMR** – adjusted for age and sex • **Model 2 – HR 3.70 (95% CI 0.93 to 14.72, P=0.06) for severe fibrosis on CMR vs. no fibrosis on CMR** – adjusted for EuroSCORE Number of deaths during follow-up was not reported either combined or separately for the individual prognostic groups. Survival status was assessed either during routine follow-up visits (n=34) or through telephone interviews with the patient or a family member, which were conducted from February 2017 to April 2017, or through death certificates (n=23). At 10 years and 9 months following AVR, patients were invited to attend follow-up studies including clinical examination, venous blood samples, echocardiography and CMR. Mean (range) follow-up: not reported, however appears that data for mortality is available for 57/58 patients and this was at ~10 years 9 months following AVR.
Comments	**All-cause mortality following AVR** Mild fibrosis vs. no fibrosis on CMR Risk of bias: 1. Study participation LOW 2. Study attrition LOW 3. Prognostic factor measurement HIGH 4. Outcome Measurement LOW 5. Study confounding LOW

Reference	**Herrmann 2018**[118]
	6. Statistical analysis HIGH 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH Indirectness: • Population – all had symptomatic severe AS and an indication for AVR, with all receiving AVR. Therefore, does not represent population where there is uncertainty about whether there is an indication for intervention. • Prognostic factor – specific severity of fibrosis on CMR compared with no fibrosis, rather than comparing any fibrosis with no fibrosis on CMR. <u>Severe fibrosis vs. no fibrosis on CMR</u> Risk of bias: 1. Study participation LOW 2. Study attrition LOW 3. Prognostic factor measurement HIGH 4. Outcome Measurement LOW 5. Study confounding LOW 6. Statistical analysis HIGH 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH Indirectness: • Population – all had symptomatic severe AS and an indication for AVR, with all receiving AVR. Therefore, does not represent population where there is uncertainty about whether there is an indication for intervention. • Prognostic factor – specific severity of fibrosis on CMR compared with no fibrosis, rather than comparing any fibrosis with no fibrosis on CMR.

Reference	**Hwang 2020**[123]
Study type and analysis	Prospective cohort study Multivariate Cox proportional hazard regression analysis South Korea
Number of participants and characteristics	N=43 Diffuse myocardial fibrosis on pre-aortic valve replacement (AVR) cardiac magnetic resonance (CMR) imaging, n=30 Normal myocardium on pre-AVR CMR, n=13 Severe aortic stenosis (AS) scheduled for isolated aortic valve replacement (AVR). Population indirectness as already indication for intervention and not within a population where there is uncertainty. **Inclusion criteria:** Severe AS scheduled for isolated AVR (without coronary artery bypass grafting). **Exclusion criteria:** ≥moderate degree of other valve disease types; contraindications to CMR; prior cardiac surgery or myocardial infarction; patients where T1 mapping was not performed. **Values listed below are presented as mean (SD) or number (%)** • Age: 65.9 (8.1) years • Male/female: 24/19 (55.8%/44.2%) • Hypertension, 24 (55.8%) • Diabetes mellitus, 7 (16.3%) • Dyslipidaemia, 9 (20.9%) • Atrial fibrillation, 7 (16.3%) • Prior percutaneous coronary intervention, 3 (7.0%) • Bicuspid aortic valve, 19 (44.2%) • Current smoker, 3 (7.0%)

Reference	**Hwang 2020[123]**
	- EuroSCORE II: 1.50 (0.87)% - Systolic blood pressure: 121.0 (18.3) mmHg - Diastolic blood pressure: 71.2 (10.4) mmHg - NYHA functional class: 2.1 (0.8) - Chest pain, 12 (27.9%) - Syncope, 6 (14.0%) - Haemoglobin: 13.6 (1.7) g/dL - Haematocrit: 40.3 (4.7)% - Estimated glomerular filtration rate: 82.2 (14.6) ml/min/1.73 m^2 - Aortic valve Vmax, pre-AVR: 4.5 (0.8) m/s - Aortic valve mean gradient, pre-AVR: 50.4 (17.3) mmHg - Aortic valve area index, pre-AVR: 0.45 (0.13) cm^2/m^2 - Aortic valve Vmax, post-AVR: 2.4 (0.5) m/s - Aortic valve mean gradient, post-AVR: 11.6 (6.4) mmHg - Aortic valve area index, post-AVR: 1.05 (0.28) cm^2/m^2 **Population source:** those matching inclusion criteria from a single centre between 2012 and 2016. Unclear if consecutive.
Prognostic variable	Diffuse myocardial fibrosis on pre- AVR CMR Normal myocardium on pre-AVR CMR (referent) Patients had CMR and echocardiography 1 month prior to AVR. CMR performed using standard protocols with LGE images and post-contrast T1 mapping acquired within 15 min following gadolinium injection. LGE-CMR images were analysed by an experienced radiologist and blinded to patient information. Region of myocardial fibrosis was defined as the sum of pixels with signal intensity >5 SDs of normal remote myocardium at each short-axis slice. Presence of midwall myocardial fibrosis was determined qualitatively by two independent experienced radiologists. No patients with infarct-pattern LGE were identified. A control group of age- and sex-matched healthy controls was included in order to categorise patients into normal myocardium and those with diffuse myocardial fibrosis. The 95% upper limit of native T1 in the control group was used for this classification, which was 1208.4 ms. Those with native T1 <1208.4 ms were considered to have normal myocardium and those with native T1 ≥1208.4 ms were considered to have diffuse myocardial fibrosis. Though this is reported for pre-AVR and post-AVR imaging, the pre-AVR value is the one relevant for this review.

Reference	**Hwang 2020[123]**
Confounders	Multivariate Cox proportional hazard regression model with backward selection analysis used for univariate markers with P-values <0.100. Factors included in adjusted analysis: atrial fibrillation, anaemia (<13 g/dL in men and <12 g/dL in women), mild renal dysfunction (eGFR <75 ml/min/1.73 m^2) and diffuse myocardial fibrosis on pre-AVR CMR. The prespecified confounder in the protocol (age) does not appear to have been included in the multivariate analysis.
Outcomes and effect sizes	**Cardiovascular death, hospitalisation for cardiac causes, non-fatal stroke and symptomatic aggravation (worsening NYHA functional class) following AVR** **HR 5.516 (95% CI 1.031 to 29.508) for diffuse myocardial fibrosis vs. normal myocardium on pre-AVR CMR** During follow-up post-AVR, 17 patients experienced the composite endpoint, which included n=2 cardiovascular deaths, n=6 hospitalisation for cardiac causes, n=1 stroke and n=15 symptom aggravation. Patients were followed for the occurrence of the composite endpoint by February 2018 using hospital records and telephone interviews. For outcome analysis using baseline CMR parameters, the date of AVR was defined as the index date to calculate time to outcomes. Median (IQR) follow-up following AVR: 38.8 (25.8-57.6) months.
Comments	**Cardiovascular death, hospitalisation for cardiac causes, non-fatal stroke and symptomatic aggravation (worsening NYHA functional class) following AVR** Risk of bias: 1. Study participation LOW 2. Study attrition HIGH 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	**Hwang 2020**[123]
	- Population – all already scheduled for AVR so does not appear to be uncertainty as to whether there is an indication for intervention - Outcome – composite outcome of multiple outcomes in protocol combined rather than reported separately - Confounding – the confounder prespecified in the protocol for this outcome (age) does not appear to have been adjusted for in the multivariate analysis. Downgraded for this as part of risk of bias rating, so not downgraded further for indirectness.

Reference	**Lee 2018**[155]
Study type and analysis	Prospective cohort study Multivariate Cox regression analysis South Korea
Number of participants and characteristics	N=127 Presence of late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR) imaging, n=41 Absence of LGE on CMR, n=86 Moderate or severe aortic stenosis (AS). Of these, 87 (69%) underwent aortic valve replacement (AVR). Of these 87 patients, 70 had surgical AVR and 17 had transcatheter AVR. Of those undergoing AVR, 82.8% had severe disease and 17.2% had moderate disease. The most common indication for AVR in moderate disease was concomitant coronary artery bypass surgery. The decision to operate was made irrespective of native T1 values on CMR. Population indirectness as in those that underwent AVR, the decision appeared to have been made prior to CMR so did not appear to be any uncertainty about whether there was indication for intervention. **Inclusion criteria:** Moderate or severe AS (transaortic peak velocity ≥3.0 m/s or transaortic mean pressure gradient ≥20 mmHg; underwent noncontrast T1 mapping on 3-T CMR **Exclusion criteria:** ≥moderate degree of other valve disease; other medical conditions with life expectancy <1 year; uninterpretable images; lost to follow-up. **Values listed below are presented as mean (SD) or number (%)** - Age: 68.8 (9.2) years

Reference	Lee 2018[155]
	• Male/female: 63/64 (49.6%/50.4%) • Body surface area: 1.67 (0.15) m^2 • Hypertension, 84 (66.1%) • Diabetes mellitus, 34 (26.8%) • Hyperlipidaemia, 36 (28.3%) • Atrial fibrillation, 15 (11.8%) • Prior coronary revascularisation, 17 (13.4%) • EuroSCORE II: 1.58 (0.99)% • Systolic blood pressure: 130.2 (18.9) mmHg • Diastolic blood pressure: 70.9 (10.8) mmHg • Heart rate: 66.6 (12.4) bpm • Any typical AS symptoms, 68 (54.5%) ○ Dyspnoea (NYHA class II-IV), 62 (48.8%) ○ Chest pain, 33 (26.0%) ○ Syncope or pre-syncope, 16 (12.6%) • Renin-angiotensin system blocker, 62 (48.8%) • Beta-blocker, 43 (44.9%) • Calcium-channel blocker, 31 (24.4%) • Diuretics, 33 (26.0%) • LV end-diastolic diameter: 49.7 (6.3) mm • LV end-systolic diameter: 31.4 (7.4) mm • Interventricular septal thickness: 11.3 (2.1) mm • Posterior wall thickness: 11.0 (2.0) mm • LV ejection fraction: 60.1 (9.7)% • Left atrial diameter: 44.3 (6.8) mm • E velocity: 0.71 (0.26) m/s • e’ velocity at septal annulus: 4.4 (1.4) cm/s • E/e’: 17.6 (8.4) • Transaortic peak velocity: 4.4 (0.8) m/s

Reference	**Lee 2018[155]**
	- Transaortic mean gradient: 48.0 (19.3) mmHg - Aortic valve area: 0.82 (0.25) cm^2 - Severe AS, 79 (62.2%) - LV end-diastolic volume on CMR: 99.1 (34.5) ml/m^2 - LV end-systolic volume on CMR: 41.6 (30.2) ml/m^2 - LV ejection fraction on CMR: 61.8 (14.1)% - LV mass index on CMR: 96.5 (35.5) g/m^2 - Presence of LGE on CMR, 41 (32.3%) - % LGE mass on CMR: 5.2 (4.8) - Native myocardial T1 value on CMR: 1232 (53) ms **Population source:** consecutive patients matching inclusion criteria between October 2011 and November 2015 at a single site.
Prognostic variable	Presence of LGE on CMR Absence of LGE on CMR (referent) All patients had CMR imaging. Prototype modified Look-Locker inversion-recovery sequence was used for noncontrast mapping of myocardial T1 relaxation time at the mid-ventricular short-axis sections of papillary muscle level, prior to administration of gadolinium contrast. Three images obtained in first and second Look-Locker segments and five in third segment. At 10 min post-gadolinium injection, phase-sensitive inversion recovery sequence was applied to image LGE on long- and short-axis images. Region of LGE was shown semi-automatically as pixels of myocardium with signal intensity >5SD of the remote normal myocardium using software. Presence of LGE was considered to indicate diffuse myocardial fibrosis present. Images were examined visually by 2 independent experienced radiologists for the presence of regional fibrosis
Confounders	Multivariate Cox regression analysis Factors included in adjusted analysis: EuroSCORE II, prior use of diuretics, presence of LGE on CMR and being within highest native T1 value tertile. Age and smoking were listed as confounding factors for these outcomes in the protocol, and neither appear to have been included in the multivariate analysis. Most underwent AVR so smoking adjustment less of an issue here (smoking was only prespecified as a confounder for nonoperative mortality), though some did not have operation.

Reference	**Lee 2018[155]**
Outcomes and effect sizes	**<u>All-cause mortality and unexpected hospitalisation for heart failure during follow-up – mixture of those that received AVR and those that did not</u>** **HR 1.56 (95% CI 1.05 to 4.37) for presence of LGE vs. absence of LGE on CMR** During follow-up, 24 events occurred. Of these, n=9 were all-cause mortality and n=15 were hospitalisations for heart failure. Of the 9 deaths, 7 were due to cardiovascular causes (n=4 acute heart failure, n=2 cardiogenic shock and n=1 ischaemic stroke). The remaining deaths were due to sepsis (n=1) and lung cancer (n=1). Of these 24 events, 20 occurred preoperatively (n=6 deaths and n=14 hospitalisations for heart failure) and 4 occurred postoperatively (n=3 deaths and n=1 hospitalisations for heart failure). All but 1 preoperative deaths were cardiovascular-related (n=1 due to lung cancer). Unplanned hospitalisation for heart failure defined as admission to hospital with signs and symptoms of decompensated heart failure requiring intravenous medication. The decision on whether to perform surgical or transcatheter AVR was made without native T1 value information by the treating physician. follow-up information was obtained via outpatient clinic visits or telephone interviews performed by the patients' clinical physicians after taking the CMR images. Median (IQR) follow-up: 27.9 (16.4-36.5) months
Comments	**<u>All-cause mortality and unexpected hospitalisation for heart failure during follow-up – mixture of those that received AVR and those that did not</u>** Risk of bias: 1. Study participation LOW 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement LOW 5. Study confounding HIGH 6. Statistical analysis HIGH 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH Indirectness: • Population – mixture of asymptomatic/symptomatic moderate and severe AS, where a large proportion were already deemed to have indications for intervention regardless of CMR results. Therefore, may not represent population where there is uncertainty in whether or not to intervene.

Reference	Lee 2018[155]
	• Outcome – composite outcome of multiple outcomes in protocol combined rather than reported separately. Also includes those with and without operation in the analysis rather than providing separately for operated and non-operated patients. • Confounding – the confounders prespecified in the protocol for this outcome (age and smoking) do not appear to have been adjusted for in the multivariate analysis. Downgraded for this as part of risk of bias rating, so not downgraded further for indirectness.

Reference	Musa 2018[187]
Study type and analysis	Prospective cohort study Multivariate Cox proportional hazards model UK
Number of participants and characteristics	N=674 (note, only 613 had data available for LV myocardial scar assessment) LV myocardial scar present on cardiac magnetic resonance (CMR) imaging – late gadolinium enhancement (LGE) present, n=341 No LV myocardial scar on CMR – LGE absent, n=272 Severe aortic stenosis (AS) scheduled for and undergoing valve intervention. Population indirectness as all already considered to have indications for intervention. Of those included in the analysis, n=399 had surgical aortic valve replacement (AVR) and n=275 had transcatheter AVR. Median time from CMR to surgical AVR was 44 days (IQR, 11-103 days) and to transcatheter AVR was 13 days (1-61 days). **Inclusion criteria:** >18 years of age; severe AS (aortic valve area <1.0 cm^2, peak pressure gradient >64 mmHg, mean pressure gradient >40 mmHg or peak velocity >4 m/s); undergone CMR for clinical or research purposes; awaiting aortic valve intervention. **Exclusion criteria:** Previous valve intervention; uninterpretable image quality; insufficient demographic data; those referred that underwent only medical management. **Values listed below are presented as mean (SD) or number (%)**

Reference	Musa 2018[187]

	LGE on CMR (myocardial scar)
	- Age, median (IQR): 74.3 (14.6) years
	- Intervention:
	  - Surgical AVR, 194 (56.9%)
	  - Transcatheter AVR, 147 (43.1%)
	- Male/female: 248/93 (72.7%/27.3%)
	- Body mass index: 27.8 (5.1) kg/m^2
	- Atrial fibrillation, 49 (14.4%)
	- Diabetes mellitus, 77 (22.6%)
	- Hypertension, 184 (54.0%)
	- Systolic blood pressure: 133.4 (20.3) mmHg
	- Diastolic blood pressure: 72.2 (11.8) mmHg
	- Bicuspid aortic valve, 80 (23.5%)
	- Known coronary artery disease, 123 (36.1%)
	- No previous percutaneous coronary intervention/coronary artery bypass grafting, 260 (76.2%)
	- Previous percutaneous coronary intervention, 38 (11.1%)
	- Previous coronary artery bypass grafting, 31 (9.1%)
	- History of myocardial infarction, 58 (17.0%)
	- STS Mortality Risk score, median (IQR): 1.74 (1.79)%
	- EuroSCORE II: 1.87 (2.85)%
	- NYHA functional class:
	  - I, 33 (9.7%)
	  - II, 138 (40.5%)
	  - III, 127 (37.2%)
	  - IV, 10 (2.9%)
	- ACE inhibitor or angiotensin-receptor blocker, 139 (40.8%)
	- Beta-blocker, 130 (38.1%)
	- Aldosterone antagonist, 21 (61.6%)
	- Statin, 224 (65.7%)

Reference	Musa 2018[187]

	- Mean aortic valve gradient, median (IQR): 46.0 (19.0) mmHg
	- Peak aortic valve gradient, median (IQR): 78.0 (30.0) mmHg
	- Aortic valve area, median (IQR): 0.70 (0.21) cm^2
	- Indexed aortic valve area, median (IQR): 0.41 (0.13) cm^2/m^2
	- Estimated pulmonary artery systolic pressure:
	  - Normal, 159 (46.6%)
	  - Moderate (31-55 mmHg), 43 (12.6%)
	  - Severe (>55 mmHg), 16 (4.7%)
	
	- LV end-diastolic volume index on CMR, median (IQR): 85.4 (33.4) ml/m^2
	- LV stroke volume index on CMR, median (IQR): 46.0 (14.9) ml/m^2
	- LV ejection fraction on CMR, median (IQR): 58.0 (21.0)%
	- Maximal wall thickness on CMR, median (IQR): 14.0 (4.0) mm
	- LV mass index on CMR, median (IQR): 87.1 (31.3) g/m^2
	- RV end-diastolic volume index on CMR, median (IQR): 68.5 (22.5) ml/m^2
	- RV ejection fraction on CMR, median (IQR): 63.8 (15.0)%
	- Indexed left atrial volume on CMR, median (IQR): 53.3 (24.4) ml/m^2
	- Aortic valve regurgitant fraction on CMR, median (IQR): 8.9 (16.2)%
	- Valvuloarterial impedance on CMR, median (IQR): 3.93 (1.3)
	- LGE pattern:
	  - Non-infarct, 222 (65.1%)
	  - Infarct, 119 (34.9%)
	- LGE mass on CMR, median (IQR): 2.72 (3.95)%
	
	<u>No LGE on CMR (no myocardial scar)</u>
	- Age, median (IQR): 75.0 (14.5) years
	- Intervention:
	  - Surgical AVR, 176 (64.7%)
	  - Transcatheter AVR, 96 (35.3%)
	- Male/female: 148/124 (54.4%/45.6%)

Reference	Musa 2018[187]
	- Body mass index: 27.3 (4.8) kg/m^2 - Atrial fibrillation, 28 (10.3%) - Diabetes mellitus, 58 (21.3%) - Hypertension, 155 (57.0%) - Systolic blood pressure: 137.3 (20.2) mmHg - Diastolic blood pressure: 74.0 (11.8) mmHg - Bicuspid aortic valve, 53 (19.4%) - Known coronary artery disease, 74 (27.2%) - No previous percutaneous coronary intervention/coronary artery bypass grafting, 220 (80.9%) - Previous percutaneous coronary intervention, 16 (5.9%) - Previous coronary artery bypass grafting, 22 (8.1%) - History of myocardial infarction, 11 (4.0%) - STS Mortality Risk score, median (IQR): 1.76 (1.69)% - EuroSCORE II: 1.64 (1.69)% - NYHA functional class: o I, 47 (17.3%) o II, 90 (33.1%) o III, 98 (36.0%) o IV, 8 (2.9%) - ACE inhibitor or angiotensin-receptor blocker, 107 (39.3%) - Beta-blocker, 92 (33.8%) - Aldosterone antagonist, 11 (4.0%) - Statin, 162 (59.6%) - Mean aortic valve gradient, median (IQR): 46.0 (17.0) mmHg - Peak aortic valve gradient, median (IQR): 79.5 (30.0) mmHg - Aortic valve area, median (IQR): 0.70 (0.17) cm^2 - Indexed aortic valve area, median (IQR): 0.40 (0.13) cm^2/m^2 - Estimated pulmonary artery systolic pressure: o Normal, 138 (50.7%)

Reference	Musa 2018[187]
	○ Moderate (31-55 mmHg), 30 (11.0%) ○ Severe (>55 mmHg), 11 (4.0%) • LV end-diastolic volume index on CMR, median (IQR): 73.3 (23.1) ml/m^2 • LV stroke volume index on CMR, median (IQR): 45.8 (14.2) ml/m^2 • LV ejection fraction on CMR, median (IQR): 64.0 (12.0)% • Maximal wall thickness on CMR, median (IQR): 13.0 (3.0) mm • LV mass index on CMR, median (IQR): 74.9 (28.5) g/m^2 • RV end-diastolic volume index on CMR, median (IQR): 66.8 (19.8) ml/m^2 • RV ejection fraction on CMR, median (IQR): 65.0 (11.0)% • Indexed left atrial volume on CMR, median (IQR): 51.4 (25.4) ml/m^2 • Aortic valve regurgitant fraction on CMR, median (IQR): 7.7 (12.2)% • Valvuloarterial impedance on CMR, median (IQR): 3.98 (1.5) **Population source:** those matching inclusion criteria referred to 6 UK cardiothoracic surgical centres between January 2003 and May 2015 following evaluation by multidisciplinary heart team. Unclear if consecutive.
Prognostic variable	LV myocardial scar present on CMR – LGE present No LV myocardial scar on CMR – LGE absent (referent) CMR performed on 1.5T and 3T scanners using standardised protocols. Cine images acquired in long-axis planes and contiguous short-axis slices for ventricular volumes, mass and function. LGE technique was used to identify myocardial scar, as previously described. All CMR scans centralised and re-reported in core laboratory by experienced readers blinded to clinical parameters. Each centre analysed a single component of the CMR scan for the entire study population according to a prespecified standard operating procedure. LGE was categorised by 2 observers into 3 patterns (no LGE, infarct LGE or non-infarct LGE) and quantified with the full width at half-maximum method as a percentage of the LV. LGE was not performed in 61/674 patients.
Confounders	Multivariate Cox proportional hazards model. Unique, clinically relevant predictor variables with P<0.10 in univariate analysis were entered into the multivariate models. Factors included in adjusted analysis: • **All-cause mortality:** RV ejection fraction on CMR, LV ejection fraction on CMR, indexed left atrial volume on CMR, atrial fibrillation, LV maximal wall thickness, STS score, LV stroke volume on CMR, coronary artery disease, aortic valve area on echocardiography, age, presence of LGE (myocardial scar) and bicuspid aortic valve.

Reference	Musa 2018[187]
	- **Cardiovascular mortality:** Gender, previous coronary artery disease, LV ejection fraction on CMR, atrial fibrillation, age and presence of LGE (myocardial scar) Various other models were reported with the inclusion of alternative variables, but the main analysis was extracted as this included the highest number of variables in the model. Age was the only confounder listed for postoperative mortality and this has been included in the multivariate model.
Outcomes and effect sizes	**All-cause mortality following AVR** **HR 2.39 (95% CI 1.40 to 4.05) for LV myocardial scar on CMR vs. LV myocardial scar on CMR** (adjusted for 11 factors) **Cardiovascular mortality following AVR** **HR 3.14 (95% CI 1.65 to 5.99) for LV myocardial scar on CMR vs. LV myocardial scar on CMR** (adjusted for 6 factors) During follow-up, 145 patients died (n=52 following surgical AVR and n=93 following transcatheter AVR). Cardiovascular cause of death was identified in 70 patients (n=19 following surgical AVR and n=51 following transcatheter AVR). At 30 days post-intervention, there were n=12 deaths (n=5 following surgical AVR and n=7 following transcatheter AVR). At 1-year, there were n=42 overall deaths (n=12 following surgical AVR and n=30 following transcatheter AVR). Patients with a myocardial scar had higher all-cause mortality (26.4% vs. 12.9%) and cardiovascular mortality (15.0% vs. 4.8%) compared to those without it. Anonymous clinical and imaging data were collected and managed with REDCap software. All deaths identified through UK NHS National Spine Database. Cardiovascular mortality was established from official death certificates, which in the UK list up to 3 causes of death and were adjudicated by 2 readers blinded to clinical data. Cardiovascular mortality was defined as death due to myocardial ischaemia and infarction, heart failure, cardiac arrest results from arrythmia or unknown cause, or cerebrovascular accident. Median (IQR) follow-up: 3.6 (2.6-5.9) years.
Comments	**All-cause mortality following AVR** Risk of bias: 1. Study participation LOW 2. Study attrition LOW 3. Prognostic factor measurement HIGH 4. Outcome Measurement LOW 5. Study confounding LOW

Reference	**Musa 2018[187]**
	6. Statistical analysis LOW 7. Other risk of bias LOW OVERALL RISK OF BIAS HIGH Indirectness: • Population – all included in analysis underwent AVR so already considered to be an indication for intervention. **Cardiovascular mortality following AVR** Risk of bias: 1. Study participation LOW 2. Study attrition LOW 3. Prognostic factor measurement HIGH 4. Outcome Measurement LOW 5. Study confounding LOW 6. Statistical analysis LOW 7. Other risk of bias LOW OVERALL RISK OF BIAS HIGH Indirectness: • Population – all included in analysis underwent AVR so already considered to be an indication for intervention.

Reference	**Rajesh 2017[225]**
Study type and analysis	Prospective cohort study Multivariate logistic regression analysis India
Number of participants and characteristics	N=109 Late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR) imaging, n=46 No LGE on CMR, n=63

Reference	Rajesh 2017[225]
	Severe aortic stenosis (AS) with or without symptoms. Contains mixture of those that had medical management only and those that underwent aortic valve replacement (AVR). In total, 38 had AVR and 71 were managed conservatively. All symptomatic severe patients were referred for AVR, whereas asymptomatic severe patients underwent conservative management. There were also some symptomatic severe patients that refused surgery and were therefore followed up under conservative management. Population indirectness as clearly already indications for intervention in a proportion of the patients (35%). **Inclusion criteria:** Adults with severe AS (indexed aortic valve area ≤0.6 cm^2/m^2 on echocardiography); CMR performed; CMR artefacts present **Exclusion criteria:** Severe concomitant aortic regurgitation; > mild involvement of other valves; cardiomyopathy; previous myocardial infarction; any contraindication to CMR, particularly estimated glomerular filtration rate ≤30 ml/min; refusal to consent. **Values listed below are presented as mean (SD) or number (%)** LGE on CMR (fibrosis present) • Age: 58.7 (12.2) years • Male/female: 27/19 (58.7%/41.3%) • NYHA class I/II, 34 (73.9%) • NYHA class III/IV, 11 (26.1%) • Smoker, 6 (13%) • Chronic obstructive pulmonary disease, 9 (19.5%) • Angiographic coronary artery disease, 20 (43.4%) • Chronic kidney disease, 3 (6.5%) • Diabetes mellitus, 5 (10.8%) • Hypertension, 24 (52.1%) • Simpsons ejection fraction: 52.8 (12.4)% • LV mass on CMR: 149.2 (28.4) g • Aortic velocity time integral: 93.6 (10.2) cms • Peak aortic velocity: 4.0 (0.5) m/s

Reference	Rajesh 2017[225]
	- Peak systolic gradient: 67.4 (20.1) mmHg - Mean gradient: 42.4 (13.2) mmHg - Valvuloarterial impedance: 4.36 (1.5) mmHg/m^2/ml - Indexed end-diastolic volume: 84 (20.4) ml/m^2 <u>No LGE on CMR (no fibrosis)</u> - Age: 56.3 (12.7) years - Male/female: 36/27 (57.1%/42.9%) - NYHA class I/II, 57 (90.4%) - NYHA class III/IV, 7 (9.6%) - Smoker, 3 (4.7%) - Chronic obstructive pulmonary disease, 9 (14.2%) - Angiographic coronary artery disease, 18 (28.5%) - Chronic kidney disease, 9 (14.2%) - Diabetes mellitus, 6 (9.5%) - Hypertension, 31 (49.2%) - Simpsons ejection fraction: 59.1 (8.5)% - LV mass on CMR: 135.4 (30.3) g - Aortic velocity time integral: 97.8 (12.3) cms - Peak aortic velocity: 4.3 (0.6) m/s - Peak systolic gradient: 77.7 (24.1) mmHg - Mean gradient: 46.3 (13.8) mmHg - Valvuloarterial impedance: 4.0 (0.8) mmHg/m^2/ml - Indexed end-diastolic volume: 82 (15.1) ml/m^2 **Population source:** those matching inclusion criteria at single centre between July 2012 and July 2015.
Prognostic variable	LGE on CMR No LGE on CMR (referent)

Reference	Rajesh 2017[225]
	CMR performed using 1.5T scanner according to standardised protocol. LGE acquired in gradient echo sequence FIESTA for static imaging. Steady-state free precession used for cine imaging. At 15 min following gadolinium injection, images were obtained in standard 2 chamber, 4 chamber and short-axis view. LGE was then analysed. Region with the lowest mean signal intensity was considered to be remote myocardium and LGE regions were considered to be >2.4 SD of the remote myocardium. Left ventricle separated into 17 segments, fibrosis patterns recorded and degree of fibrosis calculated by counting number of segments in which fibrosis was present. Fibrosis was considered to be present if LGE was observed in at least 10% of the segment by area. If fibrosis was present in a segment it was counted as 'one' and anything less than 10% was excluded. LGE patterns were described as no LGE, infarct or mid myocardial LGE. Observers were blinded to clinical and echocardiography data.
Confounders	Multivariate logistic regression analysis Factors included in adjusted analysis: age >62 years, LGE on CMR (fibrosis), NYHA class III/IV, current smoker, modified Simpsons LV ejection fraction, LV mass on CMR, peak velocity and valvuloarterial impedance Prespecified factors for operative (age) and nonoperative (age and smoking) mortality appear to have been adjusted for in the multivariate model. Age was only listed confounder prespecified for other components of the composite outcome and has been adjusted for.
Outcomes and effect sizes	**Mortality, LV ejection fraction drop ≥20%, new-onset heart failure or hospitalisation for cardiovascular causes and new-onset arrythmia – mixture of those undergoing surgery and those on conservative management** **OR 1.68 (95% CI 0.60 to 4.60) for LGE on CMR (fibrosis) vs. no LGE on CMR (no fibrosis)** During follow-up, 24 deaths occurred (n=6 postoperatively and n=18 in non-surgical group). Of postoperative deaths, n=5 were due to cardiovascular causes and n=1 was due to bleeding, with n=3 having LGE present. Of the 18 patients that died without surgery, 10 had LGE present. For the composite primary outcome, 38 events occurred during follow-up. Of these events, n=22 occurred in those with LGE present and n=16 occurred in those with no LGE present. Symptomatic patients were referred for AVR and follow-up for events prior to and following surgery was performed. Symptomatic patients that refused surgery due to personal reasons were followed up as with the asymptomatic group under conservative management. Mean (range) follow-up: 13 (6-17) months
Comments	**Mortality, LV ejection fraction drop ≥20%, new-onset heart failure or hospitalisation for cardiovascular causes and new-onset arrythmia – mixture of those undergoing surgery and those on conservative management** Risk of bias: 1. Study participation LOW

Reference	Rajesh 2017[225]
	2. Study attrition HIGH 3. Prognostic factor measurement LOW 4. Outcome Measurement HIGH 5. Study confounding LOW 6. Statistical analysis VERY HIGH 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH Indirectness: • Population – mixture of asymptomatic/symptomatic severe AS, where 35% were already deemed to have indications for intervention regardless of CMR results. Therefore, may not fully represent a population where there is uncertainty in whether or not to intervene. • Outcome – composite of multiple factors listed in protocol, as well as some not listed in protocol, rather than reporting separate analyses. Also includes some patients that were medically managed and some that underwent surgery rather than reporting results separately for different treatments.

D.3 Aortic stenosis – coronary artery disease on CT

Reference	**Carstensen 2016[40]**
Study type and analysis	Prospective cohort study Multivariable Cox regression model, **but no analysis for our variable of interest**
Number of participants and characteristics	**Total n=104** Normal coronary angiogram 18% (19) Atheromatosis 51% (53) One vessel 16% (17) Two vessel 12% (12) Three vessel 3% (3) **Inclusion criteria** Asymptomatic moderate–severe aortic stenosis (aortic valve area ,1.5 cm^2) with a peak velocity by continuous wave Doppler >2.5 m/s, defined by the treating physician, preserved LVEF ≥ 50%. No indication for AVR at baseline

Reference	Carstensen 2016[40]
	Exclusion criteria Atrial fibrillation or other severe heart valve disease **Values listed below are presented as mean (SD), median (IQR) or number (%)** **Patient characteristics:** Age: 72 (9) years Male: 68% AVA: 0.90 (0.75-1.14) cm^2 Current smoker: 17% EuroScore: 5.6 (2) Systolic blood pressure, mmHg: 145 (20) Chronic lung disease: 7% proBNP, pmol/L: 24 (13-51) **Population source**: six hospitals in the Greater Copenhagen area Consecutive sample, September 2009 – January 2012
Prognostic variable	

	N with event free survival (n=61)	**N with event (n=43)**
Normal coronary angiogram	20% (12)	16% (7)
Atheromatosis	54% (33)	47% (20)
One vessel	18% (11)	14% (6)
Two vessel	5% (3)	21% (9)
Three vessel	3% (2)	2% (1)

All patients had a thorough clinical work-up, including an electrocardiogram, lung function test, 6-minute walk test, and blood samples including pro-BNP.

By September 2013 information on mortality and indication of AVR was obtained from the electronic health record by a systematic review of hospital contacts (outpatient visits and acute admissions) after the baseline examination. The reviewer was blinded to all echocardiographic data.

<table>
<tr><th>Reference</th><th>Carstensen 2016[40]</th></tr>
<tr><td></td><td>The treating physician was blinded to the results of the echocardiographic examination and the MDCT performed in the present study and referral for AVR was performed independently by the clinical heart team.

Cardiac angiography was performed by MDCT with intravenous contrast medium. Coronary computed tomography angiography analyses were performed according to the American Society of Cardiovascular Computed Tomography guidelines.
A coronary lesion was considered significant if the stenosis was >50% of the luminal diameter.
The American Heart Association 16-segment coronary artery model, modified after Austen et al. was used.</td></tr>
<tr><td>Confounders</td><td>CAD was not reported as adjusted outcome.</td></tr>
<tr><td>Outcomes and effect sizes</td><td>**43 patients reached the endpoint of indication for AVR** and no patients experienced sudden cardiac death. The indication for AVR was reduced LVEF without symptoms in one patient and symptoms in the rest (n = 42). Median time from baseline examination to indication for AVR was 18 months (IQR 9–28). Seven patients were not operated due to cancer (2), dementia (1), excessive obesity (1), declined (2), and one patient died a sudden cardiac death awaiting AVR.
<table>
<tr><th></th><th>N with event free survival (n=61)</th><th>N with event (n=43)</th></tr>
<tr><td>Normal coronary angiogram</td><td>20% (12)</td><td>16% (7)</td></tr>
<tr><td>Atheromatosis</td><td>54% (33)</td><td>47% (20)</td></tr>
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<tr><td>Three vessel</td><td>3% (2)</td><td>2% (1)</td></tr>
</table>
Median follow-up of 2.3 years (IQR 1.7–3.6)</td></tr>
<tr><td>Comments</td><td>Risk of bias:
<table>
<tr><td>1. Study participation</td><td>HIGH</td></tr>
<tr><td>2. Study attrition</td><td>LOW</td></tr>
<tr><td>3. Prognostic factor measurement</td><td>LOW</td></tr>
<tr><td>4. Outcome Measurement</td><td>HIGH</td></tr>
<tr><td>5. Study confounding</td><td>HIGH</td></tr>
<tr><td>6. Statistical analysis</td><td>HIGH</td></tr>
<tr><td>7. Other risk of bias</td><td>LOW</td></tr>
<tr><td>OVERALL RISK OF BIAS</td><td>VERY HIGH</td></tr>
</table></td></tr>
</table>

Reference	**Carstensen 2016[40]**
	Indirectness: - None identified

Reference	**Larsen 2016[152]**
Study type and analysis	Prospective cohort study Multivariable Cox proportional hazards regression model, **but only univariate for our variable of interest**
Number of participants and characteristics	**Total n=116** CAD >70% stenosis on MDCT n = 19 (including 6 with multi-vessel disease) CAD ≤ 70% stenosis on MDCT n = 97 **Inclusion criteria** Asymptomatic aortic stenosis. Asymptomatic defined by the treating physician, with a peak velocity by continuous wave Doppler >2.5 m/s **Exclusion criteria** P-creatinine >130 mmol/l, allergy to contrast, LVEF <50% on echo or known malignant disease **Values listed below are presented as mean (SD), median (IQR) or number (%)** **Patient characteristics:** Age: 72 (8) years Male: 73% Mean AVA by TTE: 1.01 (0.30) cm^2 Current smoker: 16% Past smoker: 57% Systolic blood pressure, mmHg: 145 (20) **Population source**: six hospitals in the Greater Copenhagen area

Reference	Larsen 2016[152]
	Consecutive sample, September 2009 – January 2012
Prognostic variable	CAD >70% stenosis on MDCT All patients had a thorough clinical work-up, including an electrocardiogram, lung function test, 6-minute walk test, and blood samples including pro-BNP. By September 2013 information on mortality and indication of AVR was obtained from the electronic health record by a systematic review of hospital contacts (outpatient visits and acute admissions) after the baseline examination. The reviewer was blinded to all echocardiographic data. The treating physician was blinded to the results of the echocardiographic examination and the MDCT performed in the present study and referral for AVR was performed independently by the clinical heart team. Cardiac angiography was performed by MDCT with intravenous contrast medium. Coronary computed tomography angiography analyses were performed according to the American Society of Cardiovascular Computed Tomography guidelines. A coronary lesion was considered significant if the stenosis was >50% of the luminal diameter. The American Heart Association 16-segment coronary artery model, modified after Austen et al. was used.
Confounders	Univariate Cox regression model only for factors in our protocol
Outcomes and effect sizes	**47 patients reached the endpoint of indication for AVR** and no patients experienced sudden cardiac death. The indication for AVR was reduced LVEF without symptoms in one patient and symptoms in the rest. **Unadjusted hazard ratios for indication for AVR** 1.79 (0.93-3.44) for CAD >70% stenosis vs ≤70% Number with events in prognostic groups not reported and unable to read off reliable estimate from KM curves, as values do not match reported event rate Median follow-up of 27 (IQR 19–44) months
Comments	Risk of bias: 1. Study participation HIGH 2. Study attrition LOW

Reference	Larsen 2016[152]
	3. Prognostic factor measurement LOW 4. Outcome Measurement HIGH 5. Study confounding HIGH 6. Statistical analysis HIGH 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH Indirectness: • None identified

Reference	Utsunomiya 2013[275]
Study type and analysis	Prospective cohort study Cox regression analysis Japan
Number of participants and characteristics	N=64 Whole cohort (asymptomatic mild-severe AS) analyses (n=64) Multi-vessel obstructive coronary artery disease (CAD), n=11 No multi-vessel obstructive CAD, n=53 Asymptomatic AS. Mild or moderate in 55% and severe in 45%. **Inclusion criteria:** Asymptomatic calcific aortic stenosis (AS; peak transaortic velocity >2.5 m/s by Doppler ultrasound, calcification of aortic valve); left ventricular ejection fraction >50% on echocardiography; stable for 6 months prior to enrolment; provided informed consent for inclusion in the study. **Exclusion criteria:**

Reference	Utsunomiya 2013[275]
	Symptoms thought to be related to AS; aortic regurgitation of at least moderate severity; previous or scheduled aortic valve replacement; bicuspid aortic valve; irregular heart rhythm (e.g. atrial fibrillation); prior myocardial infarction or coronary revascularisation; serum creatinine >0.13 mmol/L. **Values listed below are presented as mean (SD) or number (%)** Overall cohort • Age: 74 (7) years • Male/female: 28/36 (44%/56%) • Systolic blood pressure: 137 (19) mmHg • Diastolic blood pressure: 74 (12) mmHg • Heart rate: 70 (10) bpm • Peak transaortic velocity: 3.75 (1.07) m/s • Peak transaortic velocity ≥4 m/s, 22 (34%) • Mean transaortic pressure gradient: 29 (18) mmHg • Aortic valve area: 1.14 (0.45) cm^2 • Left atrial volume index: 39 (12) ml/m^2 • Septal E/e': 15.2 (6.5) • Lateral E/e': 11.8 (5.3) • CCTA-derived aortic valve area: 1.36 (0.48) cm^2 • CCTA-derived LV ejection fraction: 69 (9)% • CCTA-derived LV mass index: 108 (32) g/m^2 • Multivessel obstructive CAD, 11 (17%) • AVCS, median (IQR): 723 (356-1284) **Population source:** appear to have been enrolled from a single institute. Time period unclear. Unclear if consecutive patients.
Prognostic variable	Whole cohort (asymptomatic mild-severe AS) analyses (n=64) Multi-vessel obstructive CAD

Reference	**Utsunomiya 2013[275]**
	No Multi-vessel obstructive CAD (referent) Cardiac CT angiography (CCTA) examinations were performed using multidetector-row CT scanner. Patients with heart rate ≥60 bpm were given an oral beta-blocker to achieve heart rate of 50-60 bpm. Sublingual nitroglycerin administered just before scanning. Dataset of contrast-enhanced scan reconstructed every 5% of R-R interval and transferred to a remote computer workstation. CCTA images were analysed by two experienced observers blinded to clinical and echocardiographic information. Reconstructed images through aortic valve and left ventricle were obtained using 25 cm field of view at 5% intervals throughout the cardiac cycle. <u>CAD</u> Coronary segments ≥2 mm in diameter assessed for obstructive coronary artery disease using thin-slice maximal intensity projections, volume renderings and curved multiplanar reconstructions. Obstructive CAD was defined as ≥50% stenosis or occlusion. If a coronary segment contained multiple lesions, the most severe lesion was recorded. CCTA examinations were performed within 1 week of echocardiography.
Confounders	Cox regression analysis performed, with multivariate results available for CAD prognostic factor. Factors included in adjusted analysis: <u>Whole cohort (asymptomatic mild-severe AS):</u> • Multi-vessel obstructive CAD vs. no multi-vessel obstructive CAD: ○ Age (per year), gender, baseline systolic blood pressure (per 10 mmHg), baseline diastolic blood pressure (per 10 mmHg), peak transaortic velocity ≥4 m/s, CCTA-derived aortic valve area (per 0.1 cm^2 decrease), CCTA-derived LV ejection fraction (per 10% decrease), CCTA-derived LV mass index (per 1 SD g/m^2) and AVCS (per 100) Age included in the multivariate results for multi-vessel obstructive CAD prognostic factor, though the other pre-specified confounder in the protocol (smoking) was not adjusted for.
Outcomes and effect sizes	**<u>Cardiac events – cardiac death, aortic valve replacement (AVR), non-fatal myocardial infarction and heart failure requiring urgent hospitalisation</u>** • **HR 2.70 (95% CI 0.95 to 7.65, P=0.063) for multi-vessel obstructive CAD vs. no multi-vessel obstructive CAD – whole cohort (asymptomatic mild-severe AS, n=64) –** adjusted for age, gender, baseline systolic blood pressure, baseline diastolic blood pressure, peak transaortic velocity ≥4 m/s, CCTA-derived aortic valve area, CCTA-derived LV ejection fraction, CCTA-derived LV mass index and AVCS

Reference	**Utsunomiya 2013**[275]
	During follow-up, 27 patients experienced events (n=5 cardiac deaths, n=11 AVR, n=3 non-fatal myocardial infarctions and n=8 heart failure requiring urgent hospitalisation). Coronary revascularisation performed in n=2 patients with multi-vessel obstructive CAD. Of the cardiac deaths, n=2 were due to out of hospital cardiac arrests in patients with severe AS and refusal of care, n=1 was due to proceeding angina pectoris with development of fatal myocardial infarction and n=2 were due to pump failure likely due to low output syndrome with subacute increase in shortness of breath one exertion. All patients that underwent AVR had severe AS at enrolment and reasons for AVR were rapid progression of AS with symptom deterioration (n=9) and critical AS (peak transaortic velocity >5.5 m/s) without symptoms (n=2). 2-year cardiac event-free survival was 64.6% and 2-year non-AVR cardiac event-free survival rate was 88.0%. Patients were assessed every 6 months during follow-up. Event information was obtained from telephone interviews, contact with patient physicians and hospital records. Coronary revascularisation was not included in cardiac events. Myocardial infarction was defined as typical symptoms, new pathological Q waves on electrocardiogram or elevated serum creatine kinase level. Median (IQR) follow-up for whole cohort: 29 (18-50) months.
Comments	**Cardiac events – cardiac death, aortic valve replacement (AVR), non-fatal myocardial infarction and heart failure requiring urgent hospitalisation** Multi-vessel obstructive CAD vs. no multi-vessel obstructive CAD – whole cohort (asymptomatic mild-severe AS, n=64) Risk of bias: 1. Study participation LOW 2. Study attrition HIGH 3. Prognostic factor measurement LOW 4. Outcome Measurement HIGH 5. Study confounding HIGH 6. Statistical analysis HIGH 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH Indirectness: • Population – unclear whether all represent a population where it was uncertain whether intervention is required, as includes a mixture of mild-severe asymptomatic AS, with only 45% being asymptomatic severe.

Reference	Utsunomiya 2013[275]
	• Confounding – though adjustment for one of the confounders pre-specified in the protocol has been performed (age) as well as other factors, the other pre-specified confounder for this outcome (smoking) was not included. Downgraded for this as part of risk of bias rating, so not downgraded further for indirectness. • Outcome – composite outcome consisting of multiple outcomes specified in the protocol, rather than reporting separately.

D.4 Aortic stenosis – aortic valve area (AVA) on CT

Reference	Clavel 2015[62]
Study type and analysis	Prospective cohort study Multivariable Cox proportional hazards regression model
Number of participants and characteristics	**Total n=269** AVA ≤1.2 on MDCT (n=175) AVA >1.2 (n=94) AVA ≤1.0 on MDCT (n=126) AVA >1.0 (n=143) **Inclusion criteria** AS patients who underwent comprehensive Doppler echocardiography and contrast-enhanced MDCT within the same episode of care (<3 months between evaluations). **Exclusion criteria** Children younger than 18 years of age, patients with identified rheumatic disease or endocarditis, and those with moderate or severe mitral valve disease and/or previous valve repair or replacement. **Values listed below are presented as mean (SD), median (IQR) or number (%)**

Reference	**Clavel 2015[62]**
	Patient characteristics: Age: 76 (11) years Male: 61% Systolic blood pressure, mmHg: 127 (18) NYHA class ≥3: 45% Chronic lung disease: 26% Coronary artery disease: 49% LVEF: 58 (15) % AVA: 0.94 (0.32) cm^2 **Population source**: Valvular heart disease clinic Sampling method and time frame unclear 4% lost to follow-up
Prognostic variable	AVA ≤1.2 on MDCT AVA ≤1.0 on MDCT
Confounders	Age-adjusted Charlson score index, sex, symptoms, mean gradient (ΔP), and left ventricular ejection fraction.
Outcomes and effect sizes	During a mean follow-up of 2.0 (1.4) years under medical treatment, there were 55 deaths **Adjusted hazard ratios for mortality under medical treatment (censored at time of AVR)** 3.16 (1.64–6.43) for AVA ≤1.2 vs >1.2 on MDCT 1.43 (0.77–2.64) for AVA ≤1.0 vs >1.0 on MDCT Data at 2 years for survival under medical treatment AVA ≤1.2 on MDCT (n=175) : 51 (6)% AVA >1.2 (n=94) : 89 (4)% AVA ≤1.0 on MDCT (n=126) : 53 (8)% AVA >1.0 (n=143) ; 80 (4)% Data at 4 years for survival under medical treatment

Reference	**Clavel 2015[62]**
	AVA ≤1.2 on MDCT (n=175) : 34 (9)% AVA >1.2 (n=94) : 81 (6)% AVA ≤1.0 on MDCT (n=126) : 32 (11)% AVA >1.0 (n=143) ; 71 (6)% This finding was confirmed in the entire follow-up (3.2 [2.5 years]), with further adjustment for AVR as a time-dependent variable. Outcome data were obtained from the annual visit of the patient or the patient’s charts, mailed questionnaires or scripted telephone interviews with the patients or physicians, and death certificate
Comments	Risk of bias: 1. Study participation HIGH 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement LOW 5. Study confounding LOW 6. Statistical analysis LOW 7. Other risk of bias LOW OVERALL RISK OF BIAS HIGH Indirectness: • None identified

D.5 Aortic stenosis – aortic valve calcium score on CT

Reference	**Akodad 2018[8]**
Study type and analysis	Prospective cohort study

Reference	Akodad 2018[8]
	Multivariate logistic regression France
Number of participants and characteristics	N=118 (total of n=346 in paper, separated into two groups based on generation of TAVI valve received – useable results only provided for group 1 with first generation TAVI valves, which were Corevalve and Sapien XT valves) Calcium score >6,000 Hounsfield units (HU), n= not reported Calcium score ≤6,000 HU, n= not reported Patients undergoing TAVI for aortic stenosis (AS). >50% were symptomatic (≥3 NYHA class) and mean aortic valve gradient was consistent with severe AS. Therefore, likely includes some with symptomatic severe AS, though the proportion is not clear. Population may therefore not fully represent the target population of the review. **Inclusion criteria:** Patients that underwent TAVI for AS. **Exclusion criteria:** None reported. **Values listed below are presented as mean (SD) or number (%)** <u>Those that received first generation valves in the study (Corevalve and Sapien XT) – no useable results for other group so not reported</u> • Age: 83.2 (6.4) years • Male/female: 52/66 (44%/56%) • Euroscore 1: 20.1 (11.4) • Euroscore 2: NA • Body mass index: 26.6 (5.4) kg/m^2 • Chronic renal failure, 52. (44.1%) • Hypertension, 89 (75.4%) • Dyslipidaemia, 35 (29.7%) • Diabetes mellitus, 34 (28.8%)

Reference	**Akodad 2018**[8]

	- Coronary artery disease, 59 (50.0%)
	- Peripheral arterial disease, 14 (11.9%)
	- NYHA ≥3, 60 (50.9%)
	- Mean aortic valve gradient: 48.9 (16.1) mmHg
	- LV ejection fraction: 51.9 (12.6)%
	- Main access site:
	  - Transfemoral, 108 (91.5%)
	  - Transcarotid, 1 (0.9%)
	  - Subclavian, 9 (7.6%)
	  - Transaortic, 0 (0%)
	- Valve size:
	  - 23 mm, 31 (26.3%)
	  - 26 mm, 48 (40.7%)
	  - 29 mm, 37 (31.4%)
	  - 31 mm, 2 (1.7%)
	- Mean calcium score: 4092 (2177) HU
	
	Population source: consecutive patients matching inclusion criteria at single hospital in France between November 2013 and May 2014 (received a first generation TAVI valve). Note that a second group enrolled between September 2014 and October 2016 (received new generation TAVI valves) were also discussed, but no useable results were provided for this second group.

Prognostic variable	Calcium score >6,000 HU Calcium score ≤6,000 HU (referent) Pre-intervention electrocardiogram-gated noncontrast and contrast-enhanced multislice CT scan performed within 2 weeks prior to the procedure for valve and vascular access evaluation. Stored for post-processing and calcium scoring. Region of interest was selected from upper part of LV outflow tract to the leaflet tips. Calcifications were automatically detected by software with detection cutoff from 130 HU. Aortic valve calcification was then evaluated using Agatston software on transverse view. The threshold used, >6,000 HU, was identified using cutoff analysis and had the best predictive value, and was subsequently used in the multivariate analysis.
Confounders	Multivariate logistic regression analysis. Backward selection of variables with alpha-to-exit of 0.10.

Reference	**Akodad 2018**[8]
	Factors included in adjusted analysis: not reported. Unclear which variables included in multivariate analysis, though possible that the 1 pre-specified confounder for this outcome (age) has been.
Outcomes and effect sizes	**<u>All-cause mortality, stroke, myocardial infarction, heart failure or rehospitalisation for cardiac causes – 1 month following procedure</u>** **OR 106.0 (95% CI 15.5 to 727.6, P<0.01) for >6,000 HU vs. ≤6,000 HU** During the first month, the primary endpoint occurred in 28/118 patients (23.7%). This included 4 deaths during the index hospitalisation (n=3 due to annulus rupture and n=1 due to prosthesis migration). A further 4 patients died due to heart failure during the follow-up (n=3 presented with severe aortic regurgitation and n=1 presented with moderate aortic regurgitation). **<u>Rehospitalisation – 1 month following procedure</u>** **OR 23.24 (95% CI 2.39 to 100.07, P<0.0001) for >6,000 HU vs. ≤6,000 HU** Unclear whether this captured only rehospitalisation for cardiac causes or any rehospitalisation. Data on in-hospital outcomes were collected from medical records. One-month follow-up information was obtained using a phone questionnaire. Mean (range) follow-up: not reported. Events only followed up to 1 month following procedure.
Comments	**<u>All-cause mortality, stroke, myocardial infarction, heart failure or rehospitalisation for cardiac causes – 1 month following procedure</u>** Risk of bias: 1. Study participation HIGH 2. Study attrition LOW 3. Prognostic factor measurement HIGH 4. Outcome Measurement HIGH 5. Study confounding HIGH 6. Statistical analysis HIGH 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH

Reference	**Akodad 2018[8]**
	Indirectness: - Population – unclear whether population represents target population of those where further tests are required to determine whether there is an indication for intervention, as all had TAVI. Not all had symptomatic severe AS as only ~50% with NYHA ≥3, but likely to have included some with symptomatic severe AS. - Prognostic factor – threshold of >6,000 HU used very different to that specified in protocol and was not different for men and women. Downgraded for this as part of risk of bias rating, so not downgraded further for indirectness. - Outcome – composite outcome of various outcomes included in the protocol rather than reporting them separately, as well as some additional outcomes that had not been included in the protocol. Note that follow-up was also limited to 1-month post-TAVI, though this has already been considered as part of the risk of bias assessment. - Confounding – multivariate analysis was performed, though it is unclear which variables were included. This may have included age, which was pre-specified in the protocol but this is unclear. Unlikely that smoking, the other confounder, was included. Downgraded for this as part of risk of bias rating, so not downgraded further for indirectness. **<u>Rehospitalisation – 1 month following procedure</u>** Risk of bias: 1. Study participation HIGH 2. Study attrition LOW 3. Prognostic factor measurement HIGH 4. Outcome Measurement HIGH 5. Study confounding HIGH 6. Statistical analysis HIGH 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH Indirectness: - Population – unclear whether population represents target population of those where further tests are required to determine whether there is an indication for intervention, as all had TAVI. Not all had symptomatic severe AS as only ~50% with NYHA ≥3, but likely to have included some with symptomatic severe AS. - Prognostic factor – threshold of >6,000 HU used very different to that specified in protocol and was not different for men and women. Downgraded for this as part of risk of bias rating, so not downgraded further for indirectness. - Outcome – follow-up was limited to 1-month post-TAVI, though this has already been considered as part of the risk of bias assessment.

Reference	Akodad 2018[8]
	- Confounding – multivariate analysis was performed, though it is unclear which variables were included. This may have included age, which as pre-specified in the protocol but this is unclear. Unlikely that smoking, the other confounder, was included. Downgraded for this as part of risk of bias rating, so not downgraded further for indirectness.

Reference	Aksoy 2014[9]
Study type and analysis	Retrospective cohort study Cox proportional hazards analysis USA
Number of participants and characteristics	N=51 High aortic valve calcification on CT (>2027 Agatston units), n=26 Low aortic valve calcification on CT (≤2027 Agatston units), n=25 Low-flow low-gradient severe AS (severe based on valve area <1.0 cm^2) **Inclusion criteria:** Severe AS based on valve area <1.0 cm^2 on echocardiography; low-flow low gradient AS based on ejection fraction ≤25% and mean aortic valve gradient <25 mmHg on echocardiography; concurrent chest or cardiac CT performed without contrast. **Exclusion criteria:** Not reported. **Values listed below are presented as mean (SD) or number (%)** <u>Calcium score >2027 AU</u> • Age: 78.0 (8.3) years • Male/female: 15/11 (58%/42%) • Hypertension, 26 (100%) • Hyperlipidaemia, 23 (88%)

Reference	Aksoy 2014[9]
	- Diabetes mellitus, 15 (58%) - History of myocardial infarction, 21 (81%) - History of coronary artery bypass grafting, 18 (69%) - History of atrial fibrillation, 10 (38%) - History of stroke, 4 (15%) - History of chronic obstructive pulmonary disease, 9 (34%) - Baseline creatinine: 1.6 (0.7) - Ejection fraction: 21.1 (5.2)% - Aortic valve area: 0.7 (0.1) cm^2 - Peak aortic valve pressure gradient: 39.2 (9.2) mmHg - Mean aortic valve pressure gradient: 21.3 (4.4) mmHg - Aortic insufficiency ≥3, 1 (4%) - Mitral regurgitation ≥3, 6 (23%) - Right ventricular systolic pressure: 49.5 (13.2) mmHg Calcium score ≤2027 AU - Age: 71.0 (10.1) years - Male/female: 21/4 (84%/16%) - Hypertension, 21 (84%) - Hyperlipidaemia, 20 (80%) - Diabetes mellitus, 15 (60%) - History of myocardial infarction, 21 (84%) - History of coronary artery bypass grafting, 17 (68%) - History of atrial fibrillation, 12 (48%) - History of stroke, 6 (23%) - History of chronic obstructive pulmonary disease, 2 (8%) - Baseline creatinine: 1.6 (0.8) - Ejection fraction: 20.4 (4.9)% - Aortic valve area: 0.7 (0.1) cm^2 - Peak aortic valve pressure gradient: 31.7 (10.4) mmHg

Reference	Aksoy 2014[9]
	- Mean aortic valve pressure gradient: 16.6 (4.8) mmHg - Aortic insufficiency ≥3, 1 (4%) - Mitral regurgitation ≥3, 5 (20%) - Right ventricular systolic pressure: 46.3 (15.4) mmHg **Population source:** patients from single echocardiography database at Cleveland Clinic, retrospectively reviewed data between 1st January 2000 and 26th September 2009 for those matching inclusion criteria. Consecutive patients matching criteria.
Prognostic variable	High aortic valve calcification score on CT (>2027 Agatston units) Low aortic valve calcification score on CT (≤2027 Agatston units) (referent) Aortic valve calcification on CT measured using calcium-scoring software on clinical workstation. Threshold of 130 Hounsfield units used. Single user marked calcification of aortic valve leaflets in axial view. Calcification extending to LV outflow tract, coronary arteries and aorta were excluded if they were contiguous with the calcification on the valve and only the calcium on leaflets and annulus was included in the analysis. Agatston units were used to describe total calcium score. Calcium scoring of valve using CT led to median score of 2027 AU (range, 140-9210 AU), which was used to assign patients to high- and low-calcium score groups. Mean (SD) time between echocardiograms and CT scans without contrast was 110 (220) days.
Confounders	Adjusted survival analysis said to be performed using semiparametric Cox proportional hazard modelling. Factors adjusted for the analysis included those that did or did not have AVR: baseline comorbid conditions (list not provided) and echocardiographic parameters (ejection fraction, peak aortic valve gradient and mean aortic valve gradient). Note that no adjusted data was available for the separate AVR and no AVR groups.
Outcomes and effect sizes	**Mortality during follow-up – group that did not receive AVR during follow-up (non-operative mortality) – no adjustment** Report states that in those that did not receive AVR during follow-up, a high calcium score was associated with reduced survival compared to those with low calcium scores, as demonstrated by a Kaplan-Meier plot (P-value: 0.046). Follow-up on the graph is up to ~5 years in those that did not receive AVR. Insufficient data reported to be able to estimate HR. Unclear number of events in the low and high calcium groups that underwent AVR during follow-up. Note that although all of those in this group did not receive AVR, they may instead have received valvuloplasty, as n=5 in the high calcium group and n=1 in the low calcium group were reported to have had valvuloplasty during follow-up. Note that there was also one patient in the low calcium group that did not receive AVR but received total artificial heart placement and subsequent heart transplantation.

Reference	**Aksoy 2014**[9]
	<u>**Mortality during follow-up – group that received AVR during follow-up (postoperative mortality) – no adjustment**</u> <u>30 days post-surgical AVR</u> **HR 1.00 (95% CI 0.10 to 9.64) for high calcium score vs. low calcium score** This is based on event rates of 2/11 in the low calcium group and 1/10 in the high calcium group, in those that received surgical AVR during follow-up, with a P-value of 1.0 reported in the paper. Note that although all patients in these two groups received AVR, the outcome does not represent postoperative mortality completely, as other patients received valvuloplasty or total artificial heart placement and heart transplantation, which could also be considered operative procedures. In addition, there was one additional participant in the high calcium group that received TAVI rather than surgical AVR that was not included in this analysis, as the study did not report whether they were alive within this 30-day time period. <u>Long-term data</u> An estimated HR for longer term follow-up could not be extracted due to insufficient data reported in the study, as the number of events in each group over a longer time-period was not reported. However, the report stated that the mortality of patients with high calcium scores was no different than that of those with low calcium scores during long-term follow-up, as demonstrated by a Kaplan-Meier plot (P-value: 0.39). Follow-up on the graph is up to ~9 years in those that received AVR. A total of 11 patients in the low calcium group and 10 patients in the high calcium group received surgical AVR during follow-up, with an additional patient in the high calcium group receiving TAVI. Note that although all patients in these two groups received AVR, the outcome does not represent postoperative mortality completely, as other patients received valvuloplasty or total artificial heart placement and heart transplantation, which could also be considered operative procedures. <u>**Mortality during follow-up – mixture of those that did and did not receive AVR, included as factor in MV analysis**</u> Report states that there was significantly better survival in patients with low calcium scores after adjustment for baseline comorbid conditions, ejection fraction, peak aortic valve gradient, mean aortic valve gradient and whether aortic valve replacement was performed during follow-up, as demonstrated by a Kaplan-Meier plot (P-value: 0.049). Follow-up on the graph is up to 5 years. Insufficient data reported to be able to estimate HR. Unclear number of events in the low calcium group as it was unclear whether the patient excluded for having a heart transplant did or did not experience the event, though event rate was 17/26 in the high calcium group and either 13/24 or 12/24 in the low calcium group. Though adjusted for aortic valve replacement during follow-up, other patients may have had valvuloplasty during follow-up that was not adjusted for in this analysis. Mortality assessed using Social Security Death Index and electronic medical records.

Reference	**Aksoy 2014**[9]
	A total of 30 patients died during follow-up. Of these deaths, 13 were in the low-calcium score group and 17 were in the high-calcium score group. During follow-up, 21 had surgical aortic valve replacement (11 in low-calcium group and 10 in high-calcium group) and 1 had TAVI (high-calcium group). In addition, 1 had total artificial heart placement followed by a heart transplant (low-calcium group – this patient was excluded from the analysis assessing the impact of aortic valve replacement on survival) and 6 patients had aortic balloon valvuloplasty (1 in low-calcium group and 5 in high-calcium group). Mean (range) follow-up: 908 (12-3286) days.
Comments	**Mortality during follow-up – group that received AVR during follow-up (postoperative mortality) – no adjustment** 30 days post-surgical AVR Risk of bias: 1. Study participation LOW 2. Study attrition LOW 3. Prognostic factor measurement HIGH 4. Outcome Measurement LOW 5. Study confounding VERY HIGH 6. Statistical analysis VERY HIGH 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH Indirectness: • Prognostic factor – same threshold used for men and women, rather than a separate threshold as specified in protocol • Confounding – only unadjusted effect estimate available, with no adjustment for any variables, including those specified in protocol. Downgraded for this as part of risk of bias rating, so not downgraded further for indirectness.

Reference	**Clavel 2014**[63]
Study type and analysis	Prospective cohort study Multivariate Cox proportional hazards model

Reference	**Clavel 2014**[63]
	USA, France and Canada
Number of participants and characteristics	N=794 Severe aortic valve calcification (AVC) – ≥2,065 AU in men and ≥1,274 in women, n=410 Non-severe AVC – <2,065 AU in men and <1,274 AU in women, n=384 At least mild aortic stenosis (mean gradient ≥15.0 mmHg, peak aortic jet velocity ≥2.0 m/s or aortic valve area ≤2.0 cm^2) under conservative management. Appears to be a mixture of asymptomatic and symptomatic patients. Unclear whether there is any uncertainty about whether they should undergo intervention or not at time of study. **Inclusion criteria:** At least mild aortic stenosis (mean gradient ≥15.0 mmHg, peak aortic jet velocity ≥2.0 m/s or aortic valve area ≤2.0 cm^2); underwent comprehensive Doppler echocardiography and multidetector (MD) CT within same episode of care (<3 months between evaluations). **Exclusion criteria:** <18 years old; rheumatic valve disease or endocarditis; congenital heart disease (except bicuspid aortic valve); moderate or severe aortic regurgitation or mitral valve disease; history of valve repair or implantation. **Values listed below are presented as mean (SD) or number (%)** Whole cohort – data not given separately for severe AVC and non-severe AVC • Age: 73 (12) years • Male/female: 520/274 (65%/35%) • Body mass index: 28.3 (5.9) kg/m^2 • Body surface area: 1.90 (0.24) m^2 • Systolic blood pressure: 129 (19) mmHg • Diastolic blood pressure: 71 (11) mmHg • Heart rate: 68 (13) bpm • Heart failure symptoms, 211 (27%) • Hypertension, 544 (69%) • Coronary artery disease, 347 (44%) • Diabetes, 180 (23%)

Reference	**Clavel 2014[63]**

	• Hyperlipidaemia, 534 (67%)
	• Previous coronary artery bypass grafting, 183 (23%)
	
	• Peak aortic jet velocity: 3.7 (1.0) m/s
	• Mean aortic gradient: 35 (19) mmHg
	• Aortic valve area: 1.10 (0.39) cm^2
	• Indexed aortic valve area: 0.58 (0.20) cm^2/m^2
	• LV outflow tract diameter: 2.23 (0.21) cm
	• LV ejection fraction: 60 (12)%
	• LV mass index: 118 (33) g/m^2
	• AVC, median (IQR):
	  o Men: 2,022 (1,042-3,397) AU
	  o Women: 1,103 (495-2,028) AU
	• $AVC_{density}$, median (IQR):
	  o Men: 473 (256-789) AU/cm^2
	  o Women: 318 (142-593) AU/cm^2
	• Coronary artery calcium load, median (IQR): 719 (107-1,916) AU
	
	Population source: patients recruited from 1 of 3 academic centres (Mayo Clinic, USA; Bichat Hospital, France; and University Institute of Cardiology and Pneumology, Canada). Time period not stated.

Prognostic variable	Severe AVC – ≥2,065 AU in men and ≥1,274 in women Non-severe AVC – <2,065 AU in men and <1,274 AU in women (referent) Non-contrast CT was performed using MDCT scanners. The same methods for image acquisition and interpretation were used across the three centres. Validated software used to measure aortic valve calcification (AVC) by Agatston method and expressed in arbitrary units (AU). Threshold used had previously been demonstrated to be the best cutoff for severe AVC and was therefore used in the study. Technologists and cardiologists performing CT were blinded to clinical, Doppler echocardiographic and outcome data. Median time between Doppler echocardiography and MDCT was 1 day (IQR: 0-9 days).

Reference	**Clavel 2014**[63]
Confounders	Multivariate Cox proportional hazards model. Clinically relevant variables and/or variables with a P-value of ≤0.05 on univariate analysis were included in multivariate models. Multiple models extracted as all accounted for same number of variables. Factors included in adjusted analysis: • Model 1: age, sex, NYHA class ≥III, diabetes, history of coronary artery disease, indexed aortic valve area, mean gradient and left ventricular ejection fraction • Model 2: age, sex, NYHA class ≥III, diabetes, history of coronary artery disease, absolute aortic valve area, mean gradient and left ventricular ejection fraction (indexed aortic valve area in model 1 replaced with absolute aortic valve area) • Model 3: age, sex, NYHA class ≥III, diabetes, history of coronary artery disease, absolute aortic valve area, peak aortic jet velocity (Vmax) and left ventricular ejection fraction (mean gradient in model 1 replaced with Vmax) The above factors include age which is listed in the protocol as a confounder for non-operative mortality, though the other factor listed, smoking, is not included.
Outcomes and effect sizes	**Mortality under medical treatment – up to 5 years** • **HR 1.75 (95% CI 1.04 to 2.92, P=0.03) for severe AVC vs. non-severe AVC – model 1** • **HR 1.71 (95% CI 1.05 to 2.84, P=0.03) for severe AVC vs. non-severe AVC – model 2** • **HR 1.71 (95% CI 1.02 to 2.90), P=0.04) for severe AVC vs. non-severe AVC – model 3** When aortic valve implantation occurred, follow-up was considered to have ended for this analysis. This included transcatheter or surgical aortic valve implantation. During follow-up under medical management, 115 deaths occurred (n=82 were cardiovascular-related). Overall 5-year survival post-diagnosis was 65±3% under medical management. Mean (SD) follow-up under medical management: 1.7 (2.0) years. Follow-up up to death, aortic valve implantation or ≥5 years post-diagnosis was completed in 762 patients (96%).
Comments	**Mortality under medical treatment – up to 5 years (applicable for all 3 models reported)** Risk of bias: 1. Study participation LOW 2. Study attrition HIGH 3. Prognostic factor measurement LOW 4. Outcome Measurement LOW 5. Study confounding HIGH 6. Statistical analysis LOW

Reference	Clavel 2014[63]
	7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH Indirectness: • Population – unclear whether this represents a population where there is uncertainty about whether or not intervention should be performed, or whether all underwent CT as part of the prospective study, regardless of likely treatment. • Confounding factors – though adjustment for one of the confounders pre-specified in the protocol has been performed (age) as well as other factors, the other pre-specified confounder for this outcome (smoking) was not included. Downgraded for this as part of risk of bias rating, so not downgraded further for indirectness.

Reference	Fischer-Rasokat 2020[94]
Study type and analysis	Retrospective cohort study Multivariate Cox proportional hazards model Germany
Number of participants and characteristics	N=650 High aortic valve calcification (AVC): ≥2,000 AU in men and ≥1,200 in women, n=428 Non-severe AVC – <2,000 AU in men and <1,200 AU in women, n=222 Analysis of data from a TAVI registry, referred based on local heart team decision. Appears to be a mixture of asymptomatic and symptomatic patients. Unclear whether there is any uncertainty about whether they should undergo intervention or not at time of study. **Inclusion criteria:** Severe aortic stenosis (AVAi <0.6cm/m^2) treated by the transfemoral approach with data from at last the 30-day follow-up. **Exclusion criteria:** Bicuspid aortic valve, no information on SVi or AVC. High-gradient aortic stenosis (mean pressure gradient ≥40 mmHg). *This group served as controls in the study but are not include in the analysis relevant to this review.*

Reference	**Fischer-Rasokat 2020[94]**
	Values listed below are presented as mean (SD), median (IQR) or number (%) | | **Low AVC (n=222)** | **High AVC (n=428)** | Age (years): 81 (78-85) / 82 (79-85) Female: 46.8% / 51.4% NYHA class III/IV: 86.0% / 82.9% CAD: 66.2% / 64.0% Prior MI: 17.6% / 15.2% Atrial fibrillation: 56.8% / 53.5% LVEF: 60 (45-65)% / 60 (45-65)% AVC in women (AU): 887 (680-1016) / 1848 (1487-2387) AVC in men (AU): 1542 (1251-1789) / 2903 (2411-3627) **Population source:** patients recruited one high-volume centre. Time period not stated.
Prognostic variable	High AVC: ≥2,000 AU in men and ≥1,200 in women Low AVC: <2,000 AU in men and <1,200 AU in women (referent) Non-contrast CT was performed using MDCT scanners. Validated software used to measure aortic valve calcification (AVC) by Agatston method and expressed in arbitrary units (AU). Threshold used had previously been reported.
Confounders	Multivariate Cox proportional hazards model. Baseline parameters with a P-value of <0.1 on univariate analysis were included in multivariate models. Factors included in adjusted analysis: BMI, GFR, dyslipidaemia, LV hypertrophy, mean pressure gradient, aortic valve area index, balloon expandable valve, rapid pacing, residual AR. The above factors do not include age or smoking.
Outcomes and effect sizes	<u>**All-cause mortality after TAVI – 1 year**</u> • **HR 1.320 (95% CI 0.771, 2.258) for high AVC vs. low AVC** Patients still in follow-up after 1 year were censored as alive.

Reference	Fischer-Rasokat 2020[94]
	During 1 year follow-up, 92 deaths occurred (31 in low and 61 in high AVC groups).
Comments	<u>**Mortality 1 year after TAVI**</u> Risk of bias: 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 Indirectness: • Population – all already scheduled for aortic valve intervention so no uncertainty about whether there is indication for intervention. • Confounding factors –the pre-specified confounder for this outcome (age) was not included. Downgraded for this as part of risk of bias rating, so not downgraded further for indirectness.

Reference	Larsen 2016[152]
Study type and analysis	Prospective cohort study Multivariable Cox proportional hazards regression model, **but only univariate for our variable of interest**
Number of participants and characteristics	**Total n=116** (note 1 patient not evaluated for calcium density on CT) Severe AV calcium density on MDCT (>300 AU/cm^2 for women and >475 AU/cm^2 for men), n=45 No severe AV calcium density n = 70 **Inclusion criteria** Asymptomatic aortic stenosis. Asymptomatic defined by the treating physician, with a peak velocity by continuous wave Doppler >2.5 m/s

Reference	Larsen 2016[152]
	Exclusion criteria P-creatinine >130 mmol/l, allergy to contrast, LVEF <50% on echo or known malignant disease **Values listed below are presented as mean (SD), median (IQR) or number (%)** **Patient characteristics:** Age: 72 (8) years Male: 73% Mean AVA by TTE: 1.01 (0.30) cm^2 Current smoker: 16% Past smoker: 57% Systolic blood pressure, mmHg: 145 (20) **Population source**: six hospitals in the Greater Copenhagen area Consecutive sample, September 2009 – January 2012
Prognostic variable	Severe AVC density on MDCT All patients had a thorough clinical work-up, including an electrocardiogram, lung function test, 6-minute walk test, and blood samples including pro-BNP. By September 2013 information on mortality and indication of AVR was obtained from the electronic health record by a systematic review of hospital contacts (outpatient visits and acute admissions) after the baseline examination. The reviewer was blinded to all echocardiographic data. The treating physician was blinded to the results of the echocardiographic examination and the MDCT performed in the present study and referral for AVR was performed independently by the clinical heart team. AVC was indexed by aorta annulus area (AVC density) and severe AVC density was defined as >300 AU/cm^2 for women and >475 AU/cm^2 for men. AVC by Agatston was defined as calcification of the aortic leaflets, including the attachment points of the leaflets. Calcification of the aortic wall immediately connected to the calcification of the aortic valve was also included. Careful consideration was provided to avoid including calcification from ostium of coronary arteries, the mitral annulus and the mitral valve.

Reference	**Larsen 2016**[152]
Confounders	Univariate Cox regression model only for factors in our protocol
Outcomes and effect sizes	**47 patients reached the endpoint of indication for AVR** and no patients experienced sudden cardiac death. The indication for AVR was reduced LVEF without symptoms in one patient and symptoms in the rest. **Unadjusted hazard ratios for indication for AVR** 1.0 (1.00-1.00) for severe AVC vs non-severe Number with events in prognostic groups not reported and unable to read off reliable estimate from KM curves, as values do not match reported event rate Median follow-up of 27 (IQR 19–44) months
Comments	Risk of bias: 1. Study participation HIGH 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement HIGH 5. Study confounding HIGH 6. Statistical analysis HIGH 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH Indirectness: • Indirect prognostic factor definitions • Confounding - only unadjusted effect estimate available, with no adjustment for any variables, including those specified in protocol. Downgraded for this as part of risk of bias rating, so not downgraded further for indirectness.

Reference	**Ludwig 2020**[162]
Study type and analysis	Retrospective cohort study Multivariate Cox proportional hazards model

<table>
<tr><th>Reference</th><th>Ludwig 2020[162]</th></tr>
<tr><td></td><td>Germany</td></tr>
<tr><td>Number of participants and characteristics</td><td>N=526
Low-flow, low-gradient group (n=290)
Low AVC density (1st tertile, median 361.5 [239.2-447.0] mm^3 calcium/cm^2): n=96
Moderate AVC density (2nd tertile; median 772.8 [635.9-907.7] mm^3 calcium/cm^2): n=96
High AVC density (3rd tertile; median 1672.9 [1354.9-2167.6] mm^3 calcium/cm^2): n=98

Paradoxical low-flow, low-gradient group (n=236)
Low AVC density (1st tertile; median 404.4 [226.8-549.4] mm^3 calcium/cm^2): n=79
Moderate AVC density (2nd tertile; median 936.1 [753.3-1125.0] mm^3 calcium/cm^2): n=78
High AVC density (3rd tertile; median 1745.5 [1562.9-2377.0] mm^3 calcium/cm^2): n=79

Analysis of data from a TAVI registry, referred based on inter-disciplinary heart team decision. Appears to be a mixture of asymptomatic and symptomatic patients. Unclear whether there is any uncertainty about whether they should undergo intervention or not at time of study.

Inclusion criteria:
Severe low-flow, low-gradient aortic stenosis by echo (LEF-LG: EOA ≤1.0 cm^2, transvalvular gradient <40 mmHg, SVI ≤35 ml/m^2 and LVEF <50%; or paradoxical LF-LG: EOA ≤1.0 cm^2, transvalvular gradient <40 mmHg, SVI ≤35 ml/m^2 and LVEF ≥50%)

Exclusion criteria:
Planned valve-in-valve procedure, combined percutaneous mitral valve treatment or treated with investigational transcatheter heart valves.:

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

<table>
<tr><th></th><th>Low AVC (n=222)</th><th>High AVC (n=428)</th></tr>
<tr><td>Age (years)</td><td>81 (78-85)</td><td>82 (79-85)</td></tr>
<tr><td>Female</td><td>46.8%</td><td>51.4%</td></tr>
<tr><td>NYHA class III/IV</td><td>86.0%</td><td>82.9%</td></tr>
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Reference	Ludwig 2020[162]		
	CAD	66.2%	64.0%
	Prior MI	17.6%	15.2%
	Atrial fibrillation	56.8%	53.5%
	LVEF	60 (45-65)%	60 (45-65)%
	AVC in women (AU)	887 (680-1016)	1848 (1487-2387)
	AVC in men (AU)	1542 (1251-1789)	2903 (2411-3627)
	Population source: patients recruited at one high-volume centre from 2008-2018.		
Prognostic variable	Aortic valve calcium density on CT (based on total calcium in the annular plane and the LVOT: high, medium, low (referent) Non-contrast CT was performed using MDCT scanners. Aortic valve calcification (AVC) was the composite total calcium score from the annular plane and the LVOT. The density was the ratio of AVC per aortic annulus area (cm^2).		
Confounders	Multivariate Cox proportional hazards model. Baseline parameters with a P-value of <0.25 on univariate analysis were used in a forward selection process in multivariate models. Factors included in adjusted analysis: Age, BMI, diabetes, COPD, atrial fibrillation, prior myocardial infarction (for pLFLG only), and non-TF access. The above factors do not include smoking.		
Outcomes and effect sizes	**All-cause mortality after TAVI – 3 years** • **HR for high vs moderate or low AVC density in LEF LG: 0.73 (0.60, 0.88)** • **HR for high vs moderate or low AVC density in pLFLG: 0.91 (0.73, 1.14).** **Better outcome in high calcium density group** During 1 year follow-up, 100 deaths occurred in LEF LG group (24, 38 and 38 in high, moderate and low AVC density groups, respectively) and 54 deaths occurred in PLF LG group (18, 16 and 20 in high, moderate and low AVC density groups, respectively).		
Comments	**Mortality 1 year after TAVI** Risk of bias: 1. Study participation LOW 2. Study attrition LOW 3. Prognostic factor measurement HIGH		

Reference	Ludwig 2020[162]
	4. Outcome Measurement LOW 5. Study confounding LOW 6. Statistical analysis LOW 7. Other risk of bias LOW OVERALL RISK OF BIAS HIGH Indirectness: • Population – all already scheduled for aortic valve intervention so no uncertainty about whether there is indication for intervention.

Reference	Pawade 2018[212]
Study type and analysis	Multicentre registry – appears to be mainly prospective data, though may have some retrospective elements for certain patients Data from multiple prospective cohort studies (5 studies from 3 centres) provided and also data of those being considered for TAVI and that were undergoing CT scans as part of their work up (from 5 centres). All pooled into registry used for this study. Cox proportional hazards regression UK (Scotland – 1 centre, England – 1 centre), France (3 centres), Canada (1 centre), Spain (1 centre), USA (1 centre)
Number of participants and characteristics	N=918 overall (n=431 in prospective clinical research studies and n=487 imaged as part of routine clinical care) • N=215 with outcome data in whole cohort Includes various presentations of aortic stenosis (AS), including mild-severe. Symptom status appears to vary between patients – includes some severe symptomatic and also non-severe symptomatic, as well as some where the different echocardiography measures of AS severity are not in agreement (discordant group). Overall, population likely represents target population of review as states that those where a decision to perform an intervention had already been made at the time of CT were excluded from the outcome analysis, suggesting the remaining patients included in outcome analysis were those where there was uncertainty about whether or not to refer for intervention.

Reference	**Pawade 2018[212]**
	Severe aortic valve calcification (AVC) on CT (≥1377 AU for women and ≥2062 AU for men), n= not reported Non-severe AVC on CT (<1377 AU for women and <2062 AU for men), n= not reported Severe AVC on CT (≥1274 AU for women and ≥2065 AU for men) – previously published threshold used, n= not reported Non-severe AVC on CT (<1274 AU for women and <2065 AU for men), n= not reported **Inclusion criteria:** At least mild AS (peak aortic jet velocity >2.5 m/s or mean gradient >10 mmHg); undergone electrocardiogram-gated CT calcium scoring within 3 months of echocardiogram. **Exclusion criteria:** Established rheumatic heart disease; other forms of valvular heart disease of at least moderate severity; estimated glomerular filtration rate <30 ml/min per 1.73 m^2. **Values listed below are presented as mean (SD) or number (%)** <u>Whole cohort (n=918 – data not provided separately for those with outcome data)</u> • Age: 77 (10) years • Male/female: 551/367 (60%/40%) • Body surface area: 1.88 (0.25) m^2 • Body mass index: 28 (6) kg/m^2 • Systolic blood pressure: 136 (20) mmHg • Diastolic blood pressure: 72 (12) mmHg • Heart rate: 69 (13) bpm • Possible symptoms, 643 (70%) • Hypertension, 707 (77%) • Coronary artery disease, 413 (45%) • Ever smoked, 294 (32%) • Diabetes mellitus, 257 (28%) • Hyperlipidaemia, 597 (65%) • Scan interval, median (IQR): 5 (1-25)

Reference	Pawade 2018[212]
	- Peak aortic jet velocity: 3.88 (0.90) mmHg - Peak aortic jet velocity ≥4 m/s, 468 (51%) - Mean gradient: 38 (19) mmHg - Mean gradient ≥40 mmHg, 441 (48%) - Aortic valve area: 0.90 (0.35) cm^2 - Aortic valve area ≤1.0 cm^2, 615 (67%) - Aortic valve area index: 0.48 (0.18) cm^2/m^2 - Aortic valve area index ≤0.6 cm^2, 707 (77%) - Bicuspid, 64 (7%) - LV outflow tract diameter: 2.14 (0.22) cm - LV outflow tract area: 3.60 (0.76) cm^2 - Indexed stroke volume: 42 (11) ml/m^2 - Valsalva diameter: 3.32 (0.46) cm - Tubular diameter: 3.05 (0.57) cm - Ejection fraction: 61 (8.5)% - AVC score, median (IQR): 2055 (1054-3339) AU - AVC index, median (IQR): 1088 (557-1810) AU/m^2 - AVC density, median (IQR): 580 (284-940) AU/cm^2 - AVC volume, median (IQR): 1158 (594-2189) mm^3 **Population source:** data was provided by 8 different international centres. Of these, 3 (Edinburgh, Paris and Québec) provided data from 5 prospective AS clinical research studies and 5 (Europe and USA) provided data of those being considered for TAVI and that were undergoing CT scans as part of their work up, which formed a multicentre registry used in this study. Unclear whether consecutive. Though 2 of the centres had already reported threshold results for CT AVC, data provided for this study were from distinct populations of patients that did not overlap with their original cohorts.
Prognostic variable	Severe AVC on CT (≥1377 AU for women and ≥2062 AU for men) Non-severe AVC on CT (<1377 AU for women and <2062 AU for men) (referent)

Reference	Pawade 2018[212]
	Severe AVC on CT (≥1274 AU for women and ≥2065 AU for men) – previously published threshold used Non-severe AVC on CT (<1274 AU for women and <2065 AU for men) (referent) All centres performed noncontrast CT scans from 75%-80% of R-R interval. Imaging performed on different scanners depending on centre. Some centres used beta-blockade to achieve target resting heart rate of ≤65 bpm. Imaging analysis performed at each centre using range of different software packages. Method for calcium scoring was agreed at start of study and was applied at all centres. CT-AVC scores quantified on 3 mm axial slices starting at base of the valve. Calcium originating from extravalvular structures such as mitral valve annulus, ascending aorta and coronary arteries was excluded. Total AVC in AU was calculated and indexed to body surface area (AU/m^2) or divided by LV outflow tract area on echocardiography to estimate calcium density (AU/cm^2). Optimal thresholds of CT-AVC for identifying severe AS in this study were 1377 AU for women and 2062 AU for men. These were subsequently used to assess the effect of CT-AVC on prognosis. In addition, thresholds used from a previously published study (1274 AU for women and 2065 AU for men) were also used to assess prognosis in this study.
Confounders	Multivariate Cox proportional hazards regression Factors included in adjusted analysis: • Severe AVC on CT (≥1377 AU for women and ≥2062 AU for men) vs. non-severe AVC on CT (<1377 AU for women and <2062 AU for men): age, sex, Vmax ≥4 m/s and aortic valve area <1 cm^2 • Severe AVC on CT (≥1274 AU for women and ≥2065 AU for men) vs. non-severe AVC on CT (<1274 AU for women and <2065 AU for men): age, sex, Vmax ≥4 m/s and aortic valve area <1 cm^2 One of the pre-specified confounders (age) was included in the multivariate analysis for both thresholds. However, the other (smoking) was not included, though a number of other factors were included.
Outcomes and effect sizes	<u>**Death or aortic valve replacement (AVR) during follow-up – whole cohort, n=219 – adjusted for age, sex, Vmax ≥4 m/s and aortic valve area <1 cm^2**</u> **HR 3.90 (95% CI 2.19 to 6.78, P<0.001) for severe AVC on CT (≥1377 AU for women and ≥2062 AU for men) vs. non-severe AVC on CT (<1377 AU for women and <2062 AU for men)** **HR 3.80 (95% CI 2.16 to 6.69, P<0.001) for severe AVC on CT (≥1274 AU for women and ≥2065 AU for men) vs. non-severe AVC on CT (<1274 AU for women and <2065 AU for men)**

Reference	Pawade 2018[212]
	A total of 79 patients experienced events in the whole cohort (n=59 underwent AVR and n=20 deaths). AVR included surgical procedures and transcatheter AVR. Decisions about whether to proceed to AVR were made according to international clinical guidelines, independent of CT-AVC and after multidisciplinary discussion – this definition suggests that AVR events captured were not planned just prior to CT, though may have been planned following CT rather than being an emergency intervention. Patients in whom a decision to refer for AVR had already been made at the time of CT-AVC or who had CT imaging performed as part of the work up before transcatheter AVR or surgery were excluded from the outcome analysis. Median (IQR) follow-up for whole cohort: 1029 (126-2251) days.
Comments	<u>**Death or AVR during follow-up – whole cohort, n=219 – thresholds of 1377 AU for women and 2062 AU for men**</u> Risk of bias: 1. Study participation HIGH 2. Study attrition HIGH 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: • Outcome – composite outcome of two separate outcomes listed in the protocol, rather than reporting them separately. Unclear whether AVR outcome represents unplanned intervention as specified in our protocol, as some may have been emergency operations while others may have been planned following results of CT scan and discussion with team. • Confounding – though adjustment for one of the confounders pre-specified in the protocol has been performed (age) as well as other factors, the other pre-specified confounder for this outcome (smoking) was not included. Downgraded for this as part of risk of bias rating, so not downgraded further for indirectness. <u>**Death or AVR during follow-up – whole cohort, n=219 – thresholds of 1274 AU for women and 2065 AU for men**</u> Risk of bias: 1. Study participation HIGH

Reference	Pawade 2018[212]
	2. Study attrition HIGH 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: • Outcome – composite outcome of two separate outcomes listed in the protocol, rather than reporting them separately. Unclear whether AVR outcome represents unplanned intervention as specified in our protocol, as some may have been emergency operations while others may have been planned following results of CT scan and discussion with team. • Confounding – though adjustment for one of the confounders pre-specified in the protocol has been performed (age) as well as other factors, the other pre-specified confounder for this outcome (smoking) was not included. Downgraded for this as part of risk of bias rating, so not downgraded further for indirectness.

Reference	Utsunomiya 2013[275]
Study type and analysis	Prospective cohort study Cox regression analysis Japan
Number of participants and characteristics	N=64 Whole cohort (asymptomatic mild-severe AS) analyses (n=64) Aortic valve calcium (AVC) score (AVCS) ≥723, n=32 AVCS <723, n=32 Asymptomatic severe AS subgroup analyses (n=29) AVCS ≥1266, n=14 AVCS <1266, n=15

Reference	Utsunomiya 2013[275]
	Asymptomatic AS. Mild or moderate in 55% and severe in 45%. **Inclusion criteria:** Asymptomatic calcific aortic stenosis (AS; peak transaortic velocity >2.5 m/s by Doppler ultrasound, calcification of aortic valve); left ventricular ejection fraction >50% on echocardiography; stable for 6 months prior to enrolment; provided informed consent for inclusion in the study. **Exclusion criteria:** Symptoms thought to be related to AS; aortic regurgitation of at least moderate severity; previous or scheduled aortic valve replacement; bicuspid aortic valve; irregular heart rhythm (e.g. atrial fibrillation); prior myocardial infarction or coronary revascularisation; serum creatinine >0.13 mmol/L. **Values listed below are presented as mean (SD) or number (%)** Overall cohort • Age: 74 (7) years • Male/female: 28/36 (44%/56%) • Systolic blood pressure: 137 (19) mmHg • Diastolic blood pressure: 74 (12) mmHg • Heart rate: 70 (10) bpm • Peak transaortic velocity: 3.75 (1.07) m/s • Peak transaortic velocity ≥4 m/s, 22 (34%) • Mean transaortic pressure gradient: 29 (18) mmHg • Aortic valve area: 1.14 (0.45) cm^2 • Left atrial volume index: 39 (12) ml/m^2 • Septal E/e’: 15.2 (6.5) • Lateral E/e’: 11.8 (5.3)

Reference	**Utsunomiya 2013[275]**
	• CCTA-derived aortic valve area: 1.36 (0.48) cm^2 • CCTA-derived LV ejection fraction: 69 (9)% • CCTA-derived LV mass index: 108 (32) g/m^2 • Multivessel obstructive CAD, 11 (17%) • AVCS, median (IQR): 723 (356-1284) <u>AVCS ≥723</u> • Age: 75 (7) years • Male/female: 18/14 (56%/44%) • Systolic blood pressure: 141 (21) mmHg • Diastolic blood pressure: 76 (14) mmHg • Heart rate: 71 (9) bpm • Peak transaortic velocity: 4.24 (0.86) m/s • Peak transaortic velocity ≥4 m/s, 20 (63%) • Mean transaortic pressure gradient: 39 (17) mmHg • Aortic valve area: 0.83 (0.27) cm^2 • Left atrial volume index: 43 (12) ml/m^2 • Septal E/e': 16.1 (6.4) • Lateral E/e': 13.3 (6.2) • CCTA-derived aortic valve area: 1.04 (0.32) cm^2 • CCTA-derived LV ejection fraction: 67 (9)% • CCTA-derived LV mass index: 123 (35) g/m^2 • Multivessel obstructive CAD, 7 (22%) • AVCS, median (IQR): 1266 (902-1569) <u>AVCS <723</u> • Age: 73 (7) years

Reference	Utsunomiya 2013[275]
	- Male/female: 10/22 (31%/69%) - Systolic blood pressure: 133 (17) mmHg - Diastolic blood pressure: 72 (11) mmHg - Heart rate: 70 (10) bpm - Peak transaortic velocity: 3.07 (0.48) m/s - Peak transaortic velocity ≥4 m/s, 2 (6%) - Mean transaortic pressure gradient: 18 (11) mmHg - Aortic valve area: 1.45 (0.37) cm^2 - Left atrial volume index: 35 (11) ml/m^2 - Septal E/e’: 14.2 (6.6) - Lateral E/e’: 10.3 (3.8) - CCTA-derived aortic valve area: 1.68 (0.39) cm^2 - CCTA-derived LV ejection fraction: 71 (9)% - CCTA-derived LV mass index: 93 (19) g/m^2 - Multivessel obstructive CAD, 4 (13%) - AVCS, median (IQR): 361 (265-574) **Population source:** appear to have been enrolled from a single institute. Time period unclear. Unclear if consecutive patients.
Prognostic variable	<u>Whole cohort (asymptomatic mild-severe AS) analyses (n=64)</u> AVCS ≥723 AVCS <723 (referent) <u>Asymptomatic severe AS subgroup analyses (n=29)</u> AVCS ≥1266 AVCS <1266 (referent) Cardiac CT angiography (CCTA) examinations were performed using multidetector-row CT scanner. Patients with heart rate ≥60 bpm were given an oral beta-blocker to achieve heart rate of 50-60 bpm. Sublingual nitroglycerin administered just before scanning. Dataset of contrast-enhanced scan reconstructed every 5% of R-R interval and transferred to a remote computer workstation. CCTA images

Reference	Utsunomiya 2013[275]
	were analysed by two experienced observers blinded to clinical and echocardiographic information. Reconstructed images through aortic valve and left ventricle were obtained using 25 cm field of view at 5% intervals throughout the cardiac cycle. AVC AVC qualitatively assessed using non-contrast axial images. AVCS was calculated using Agatston method and coronary calcium score. AVC was defined as calcification of the aortic valve leaflets just inferior to the origins of the coronary arteries, including the attachment points of the leaflets. Calcification of the aortic wall immediately connected to calcification of aortic valve leaflets was included in AVC. Threshold used for AVCS was based on the median value in the study, which was 723 for the whole cohort and 1266 for the asymptomatic severe subgroup. CCTA examinations were performed within 1 week of echocardiography.
Confounders	Cox regression analysis performed, with multivariate results not available for AVCS thresholds. For AVCS thresholds, estimates of a univariate HR were calculated using information provided in the Kaplan-Meier plots. Factors included in adjusted analysis: Whole cohort (asymptomatic mild-severe AS): • AVCS ≥723 vs. AVCS <723: unadjusted as calculated from information reported in the paper. Asymptomatic severe AS subgroup: • AVCS ≥1266 vs. AVCS <1266: unadjusted as calculated from information reported in the paper. For AVCS threshold prognostic factors, no adjustment for any of the factors listed in the protocol was performed.
Outcomes and effect sizes	**Cardiac events – cardiac death, aortic valve replacement (AVR), non-fatal myocardial infarction and heart failure requiring urgent hospitalisation** • **HR 6.08 (95% CI 2.86 to 12.92) for AVCS ≥723 vs. AVCS <723 – whole cohort (asymptomatic mild-severe AS, n=64)** • **HR 1.71 (95% CI 0.71 to 4.15) for AVCS ≥1266 vs. AVCS <1266 – asymptomatic severe AS subgroup (n=29)** **Non-AVR cardiac events – cardiac death, non-fatal myocardial infarction and heart failure requiring urgent hospitalisation** • **HR 3.69 (95% CI 1.39 to 9.84) for AVCS ≥723 vs. AVCS <723 – whole cohort (asymptomatic mild-severe AS, n=64)** • **HR 3.08 (95% CI 0.85 to 11.23) for AVCS ≥1266 vs. AVCS <1266 – asymptomatic severe AS subgroup (n=29)**

Reference	**Utsunomiya 2013[275]**
	During follow-up, 27 patients experienced events (n=5 cardiac deaths, n=11 AVR, n=3 non-fatal myocardial infarctions and n=8 heart failure requiring urgent hospitalisation). Coronary revascularisation performed in n=2 patients with multi-vessel obstructive CAD. Of the cardiac deaths, n=2 were due to out of hospital cardiac arrests in patients with severe AS and refusal of care, n=1 was due to proceeding angina pectoris with development of fatal myocardial infarction and n=2 were due to pump failure likely due to low output syndrome with subacute increase in shortness of breath one exertion. All patients that underwent AVR had severe AS at enrolment and reasons for AVR were rapid progression of AS with symptom deterioration (n=9) and critical AS (peak transaortic velocity >5.5 m/s) without symptoms (n=2). 2-year cardiac event-free survival was 64.6% and 2-year non-AVR cardiac event-free survival rate was 88.0%. <u>AVCS</u> 2-year cardiac event-free survival was 10.8% in those with AVCS ≥723 and 85.8% in those with AVCS <723. 2-year non-AVR cardiac event-free survival was also lower in AVCS ≥723 group compared with AVCS <723 group. In separate analyses for asymptomatic severe and asymptomatic mild-moderate AS, event-free survival was lower in patients with AVCS above median compared with those below the median value, for both cardiac events overall and non-AVR cardiac events. Patients were assessed every 6 months during follow-up. Event information was obtained from telephone interviews, contact with patient physicians and hospital records. Coronary revascularisation was not included in cardiac events. Myocardial infarction was defined as typical symptoms, new pathological Q waves on electrocardiogram or elevated serum creatine kinase level. Median (IQR) follow-up for whole cohort: 29 (18-50) months. Not reported separately for asymptomatic severe subgroup.
Comments	**<u>Cardiac events – cardiac death, aortic valve replacement (AVR), non-fatal myocardial infarction and heart failure requiring urgent hospitalisation</u>** <u>AVCS ≥723 vs. AVCS <723 – whole cohort (asymptomatic mild-severe AS, n=64)</u> Risk of bias: 1. Study participation LOW 2. Study attrition HIGH 3. Prognostic factor measurement HIGH 4. Outcome Measurement HIGH 5. Study confounding VERY HIGH 6. Statistical analysis HIGH 7. Other risk of bias LOW

Reference	Utsunomiya 2013[275]
	OVERALL RISK OF BIAS VERY HIGH Indirectness: • Population – unclear whether all represent a population where it was uncertain whether intervention is required, as includes a mixture of mild-severe asymptomatic AS, with only 45% being asymptomatic severe. • Prognostic factor – threshold based on median value and is the same for men and women, whereas ideally a separate threshold would be used for men and women, and the threshold is quite different to that specified in the protocol. Downgraded for this as part of risk of bias rating, so not downgraded further for indirectness. • Confounding – results for this prognostic factor are unadjusted as no multivariate results using this threshold were reported. Pre-specified factors in the protocol have therefore not been taken into account. Downgraded for this as part of risk of bias rating, so not downgraded further for indirectness. • Outcome – composite outcome consisting of multiple outcomes specified in the protocol, rather than reporting separately. <u>AVCS ≥1266 vs. AVCS <1266 – asymptomatic severe AS subgroup (n=29)</u> Risk of bias: 1. Study participation LOW 2. Study attrition HIGH 3. Prognostic factor measurement HIGH 4. Outcome Measurement HIGH 5. Study confounding VERY HIGH 6. Statistical analysis HIGH 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH Indirectness: • Prognostic factor – threshold based on median value and is the same for men and women, whereas ideally a separate threshold would be used for men and women, and the threshold is quite different to that specified in the protocol. Downgraded for this as part of risk of bias rating, so not downgraded further for indirectness. • Confounding – results for this prognostic factor are unadjusted as no multivariate results using this threshold were reported. Pre-specified factors in the protocol have therefore not been taken into account. Downgraded for this as part of risk of bias rating, so not downgraded further for indirectness. • Outcome – composite outcome consisting of multiple outcomes specified in the protocol, rather than reporting separately.

Reference	**Utsunomiya 2013[275]**
	Non-AVR cardiac events – cardiac death, non-fatal myocardial infarction and heart failure requiring urgent hospitalisation AVCS ≥723 vs. AVCS <723 – whole cohort (asymptomatic mild-severe AS, n=64) Risk of bias: 1. Study participation LOW 2. Study attrition HIGH 3. Prognostic factor measurement HIGH 4. Outcome Measurement LOW 5. Study confounding VERY HIGH 6. Statistical analysis HIGH 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH Indirectness: • Population – unclear whether all represent a population where it was uncertain whether intervention is required, as includes a mixture of mild-severe asymptomatic AS, with only 45% being asymptomatic severe. • Prognostic factor – threshold based on median value and is the same for men and women, whereas ideally a separate threshold would be used for men and women, and the threshold is quite different to that specified in the protocol. Downgraded for this as part of risk of bias rating, so not downgraded further for indirectness. • Confounding – results for this prognostic factor are unadjusted as no multivariate results using this threshold were reported. Pre-specified factors in the protocol have therefore not been taken into account. Downgraded for this as part of risk of bias rating, so not downgraded further for indirectness. • Outcome – composite outcome consisting of multiple outcomes specified in the protocol, rather than reporting separately. AVCS ≥1266 vs. AVCS <1266 – asymptomatic severe AS subgroup (n=29) Risk of bias: 1. Study participation LOW 2. Study attrition HIGH 3. Prognostic factor measurement HIGH 4. Outcome Measurement LOW

Reference	Utsunomiya 2013[275]
	5. Study confounding VERY HIGH 6. Statistical analysis HIGH 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH Indirectness: • Prognostic factor – threshold based on median value and is the same for men and women, whereas ideally a separate threshold would be used for men and women, and the threshold is quite different to that specified in the protocol. Downgraded for this as part of risk of bias rating, so not downgraded further for indirectness. • Confounding – results for this prognostic factor are unadjusted as no multivariate results using this threshold were reported. Pre-specified factors in the protocol have therefore not been taken into account. Downgraded for this as part of risk of bias rating, so not downgraded further for indirectness. • Outcome – composite outcome consisting of multiple outcomes specified in the protocol, rather than reporting separately.

Reference	Yoon 2020[291]
Study type and analysis	Retrospective and prospective cohort study (retrospective for cases performed before participation in the registry) Multivariate Cox proportional hazards model Denmark, France, Germany, Israel, Italy, the Netherlands, Switzerland, and USA
Number of participants and characteristics	N=1034 Numbers in risk groups not stated. **Inclusion criteria:** Bicuspid aortic valve undergoing TAVI for symptomatic severe AS **Exclusion criteria:** Suboptimal CT images, non-bicuspid aortic valve **Values listed below are presented as mean (SD), median (IQR) or number (%)**

Reference	Yoon 2020[291]
	Age (years) 74.7 (9.3) Male 59.0% NYHA class III/IV 71.2% Prior MI 11.5% Prior atrial fibrillation 18.1% LVEF 53.5 (15.3)% Transfemoral access 94.3% **Population source:** consecutive patients recruited from 24 cardiovascular centres across 8 countries. Time period not stated. Median follow-up 360 (100-575) days.
Prognostic variable	Excess leaflet calcification on CT: more than the median value for the cohort, >382 mm^3; ≤382 mm^3 (referent). Numbers in each group not stated. Intra- and inter-observer agreement for leaflet calcification had ICC of 0.999 and 0.999
Confounders	Multivariate Cox proportional hazards model. Baseline parameters with a P-value of <0.1 on univariate analysis were included in multivariate models. Factors included in adjusted analysis: Age, STS score, peripheral vascular disease, prior AF, calcified raphe, aortopathy, non-TF access.
Outcomes and effect sizes	**All-cause mortality after TAVI – 2 years** • **HR for high vs low AVC density: 2.33 (1.41, 3.85)** **Cardiovascular mortality after TAVI – 2 years** • **HR for high vs low AVC density: 2.83 (1.38, 5.81)** During 1 year follow-up, 86 deaths occurred. 2-year all-cause mortality was 18.9% in those with excess leaflet calcification and 6.5% in those with mild calcification.
Comments	**All-cause mortality 2 years after TAVI** Risk of bias: 1. Study participation HIGH

Reference	Yoon 2020[291]
	2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement LOW 5. Study confounding LOW 6. Statistical analysis LOW 7. Other risk of bias LOW OVERALL RISK OF BIAS HIGH **<u>Cardiovascular mortality 2 years after TAVI</u>** Risk of bias: 1. Study participation HIGH 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement HIGH 5. Study confounding LOW 6. Statistical analysis HIGH 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH Indirectness: • Population – all already scheduled for aortic valve intervention so no uncertainty about whether there is indication for intervention.

D.6 Aortic regurgitation – regurgitant fraction and volume on cardiac MRI

Reference	**Kockova 2019[140]**
Study type and analysis	Prospective cohort study Multivariable Cox proportional hazards regression model
Number of participants and characteristics	**Total n=104** 3 failed to complete the MRI because of claustrophobia or spine deformity CMR-derived regurgitant volume <45 (n=?) and ≥45 ml (n=?). CMR-derived regurgitant fraction <34% (n=?) and ≥34% (n=?). **Inclusion criteria** (1) severe AR defined by using the integrative 2D ECHO approach; (2) absence of symptoms validated using bicycle ergometry; (3) preserved LVEF (>50%); (4) non-dilated LV end-diastolic diameter (≤70 mm) and LV end-systolic diameter index (≤25 mm/m^2); and (5) sinus rhythm. **Exclusion criteria** Guideline indications for AV intervention, acute AR, aortic dissection, endocarditis, irregular heart rate, associated with more than mild valvular disease, complex congenital heart disease, intracardiac shunt, creatinine clearance <30 mL/min, pregnancy, or contra indication for MRI **Values listed below are presented as mean (SD), median (IQR) or number (%)** **Patient characteristics:** Age: 44 (13) years Male (%) 86% Smoker (%) 13% CAD 4% NYHA class I (%) 100% Systolic blood pressure, mmHg: 136 (16) LVEF on 2D echo 64 (6)% Moderate-to-severe AR 54% Severe AR 46%

Reference	**Kockova 2019**[140]
	Population source: Consecutive patients from three tertiary cardiology centres Enrolment from March 2015 to September 2018; follow up assessment every 6 months to 30 September 2018 Median follow-up of 587 days (IQR) 296–901 days, The follow-up data on AV interventions, mortality, and cardiac hospitalizations were obtained in all patients (100%) using population registry, medical files, and contact with referring physicians or family.
Prognostic variable	CMR-derived regurgitant volume ≥45 ml vs <45 CMR-derived regurgitant fraction ≥34% vs <34
Confounders	MRI-derived LV volumes or their indices.
Outcomes and effect sizes	Aortic valve surgery 0 deaths occurred A total of 20 (19%) individuals underwent AV surgery while the remaining patients were treated conservatively. **Adjusted hazard ratios for event-free survival** 1.03 (1.01−1.04) for RV ≥45 ml vs <45 on CMR 1.05 (1.02−1.08) for RF ≥34% vs <34 on CMR
Comments	Risk of bias: 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 Indirectness: • None identified

<table>
<tr><th>Reference</th><th>Myerson 2012[191]</th></tr>
<tr><td>Study type and analysis</td><td>Retrospective cohort study
Multivariable Cox proportional hazards regression model and multiple logistic regression</td></tr>
<tr><td>Number of participants and characteristics</td><td>**Total n=113**
Aortic regurgitant fraction measured by CMR ≤33% (n=74) and >33% (n=39), (scan with highest regurgitant fraction used as the baseline).
CMR-derived regurgitant volume ≤42 (n=?) and >42 ml (n=?).

Inclusion criteria
Patients at least 18 years of age, asymptomatic with moderate or severe chronic AR on echocardiography by standard (semi-quantitative) assessment

Exclusion criteria
Presence of other significant valve disease or clinical or angiographic evidence for coronary disease

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

Patient characteristics:
<table>
<tr><th></th><th>Conservative Mx</th><th>Requiring surgery</th></tr>
<tr><td>Age:</td><td>50.8 (16.8) years</td><td>45.7 (18.7)</td></tr>
<tr><td>Systolic blood pressure, mmHg:</td><td>132.9 (19.3)</td><td>134.2 (16.0)</td></tr>
<tr><td>LVEF:</td><td>63.6 (8.7) %</td><td>62.9 (6.4)%</td></tr>
<tr><td>Regurgitant volume (ml):</td><td>27.5 (15.5)</td><td>74.7 (28.5)</td></tr>
<tr><td>Regurgitant fraction (%)</td><td>21.8 (9.8)</td><td>42.0 (9.5)</td></tr>
</table>
Population source: 4 high-volume CMR centres in Oxford, London, Leeds (United Kingdom), and Auckland (New Zealand).
Time frame for sampling unclear
Follow up was up to 9 years (mean 2.6±2.1 years)
In Oxford, patients participated in a research study, with annual CMR scans, and clinical decisions were made without knowledge of the CMR data. In the other 3 centres study patients were identified from the clinical CMR databases (although they were initially diagnosed with echocardiography) and clinicians had access to the CMR data.</td></tr>
</table>

Reference	**Myerson 2012**[191]
Prognostic variable	Aortic regurgitant fraction measured by CMR >33% (n=39) vs ≤33% (n=74) CMR-derived regurgitant volume >42 ml (n= not reported) vs ≤42 (n= not reported).
Confounders	Unclear, likely RF, RV and LVEDV
Outcomes and effect sizes	Thirty-nine patients (35%) underwent aortic valve replacement during the follow-up period, having developed symptoms (n=19) or other established echocardiographic indications for surgery (excessive LV dilation, n=17; or reduced LV function [echocardiographic ejection fraction <50%], n=3). RF ≤33% survival 93% RF >33% survival 34% **Adjusted hazard ratios for indication for developing indication for surgery (initially asymptomatic)** 7.4 (3.0 to 18.6) for RF >33% vs ≤33 on CMR 13.2 (3.8 to 45.8) for RV >42 on vs ≤42 CMR Events were only counted if the reason for aortic valve surgery was for established indications (primarily symptoms, excess LV dilation, or LV dysfunction). A minimum period of 2 months was required between the CMR scan and the decision for surgery to avoid the potential bias of patients having a CMR scan en route to surgery that had already been planned.
Comments	Risk of bias: 1. Study participation HIGH 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement HIGH 5. Study confounding HIGH 6. Statistical analysis LOW 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH Indirectness: • None identified

D.7 Mitral regurgitation – regurgitant volume on cardiac MRI

<table>
<tr><th>Reference</th><th>Myerson 2016[190]</th></tr>
<tr><td>Study type and analysis</td><td>Prospective cohort study
Cox proportional hazards regression model</td></tr>
<tr><td>Number of participants and characteristics</td><td>Total n=109
Censored at the point of surgery
CMR-derived regurgitant volume ≤55 (n=80) and >55 ml (n=29).
CMR-derived regurgitant fraction ≤40% (n=67) and >40% (n=42).

Inclusion criteria
Asymptomatic patients with moderate or severe chronic organic mitral regurgitation on echocardiography

Exclusion criteria
‘Functional’ mitral regurgitation (secondary to annular dilation or LV dysfunction), other significant valve disease and clinical and/or angiographic evidence of coronary disease.

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

Patient characteristics:
<table>
<tr><th></th><th>Conservative Mx (n=84)</th><th>Requiring surgery (n=25)</th></tr>
<tr><td>Age (years):</td><td>65.1 (14.9)</td><td>63.8 (12.6)</td></tr>
<tr><td>Male (%)</td><td>65</td><td>76</td></tr>
<tr><td>Systolic blood pressure, mmHg:</td><td>143.9 (23.1)</td><td>132.1 (20.1)</td></tr>
<tr><td>LVEF:</td><td>66.9 (7.6)%</td><td>63.9 (7.4)%</td></tr>
<tr><td>Regurgitant volume (ml):</td><td>39.4 (20.0)</td><td>65.9 (23.7)</td></tr>
</table>
</td></tr>
</table>

Reference	**Myerson 2016**[190]
	Regurgitant fraction (%) 32.1 (12.4) 45.7 (11.7) **Population source**: Consecutive patients from four high-volume CMR centres in Oxford, Leeds, London (UK) and Auckland (New Zealand). Recruitment period unclear Follow up was up to 8 years (mean 2.5 ± SD 1.9 years; median 1.6 years) In Oxford, patients participated in a research study, with annual CMR scans, and clinical decisions were made without knowledge of the CMR data. In the other 3 centres study patients were identified from the clinical CMR databases (although they were initially diagnosed with echocardiography) and clinicians had access to the CMR data.
Prognostic variable	CMR-derived regurgitant volume ≤55 (n=80) and >55 ml (n=29). CMR-derived regurgitant fraction ≤40% (n=67) and >40% (n=42).
Confounders	N/A
Outcomes and effect sizes	Indication for surgery Twenty five patients (23%) underwent mitral valve repair/replacement during the follow-up period (the ‘crossover’ group), having developed symptoms (n=19) or other established echocardiographic indications for surgery (excessive LV dilation [ESD >4.0cm], n=4; or pulmonary hypertension [>50mmHg] with a repairable valve, n=2) Subjects with a regurgitant volume <55ml had a very high chance of remaining free of symptoms or surgery: 95% at the median time (1.6 years) and 91% at 5 years. This contrasted with 54% at 1.6 years and 21% at 5 years for patients with regurgitant volume >55m **Unadjusted hazard ratios for indication for surgery up to 5 years** 0.20 (0.09−0.45) for RV ≤55 vs >55 ml on CMR Unable to calculate HR for RF because data divided into three subgroups A minimum period of 2 months was required between the CMR scan and the decision for surgery to avoid the potential bias of patients having a CMR scan en route to surgery that had already been planned.
Comments	Risk of bias:

Reference	**Myerson 2016**[190]
	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: • None identified

Reference	**Penicka 2018**[213]
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

Reference	Penicka 2018[213]
	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 Follow up median 5.0 years (IQR 3.5–6.0 years) Clinical decisions were made without knowledge of the CMR data. Analysis was performed by an operator blinded to the results of echocardiographic assessment and the symptomatic status of the patient.
Prognostic variable	CMR-derived regurgitant volume (continuous variable: per 10ml increase)
Confounders	Age, sex and MRI-derived LVESVI
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** 1.10 (1.05–1.20) for RV on CMR **Adjusted hazard ratio for indication for mitral valve surgery** 1.23 (1.06–1.29) for RV on CMR According to the Youden index, the optimal cut-off of RV to predict mortality and its combination with the development of indication for mitral valve surgery was ≥50 mL.
Comments	Risk of bias (both outcomes): 1. Study participation LOW

Reference	**Penicka 2018**[213]
	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: • Prognostic factor indirectness: only reported as a continuous variable

D.8 Tricuspid regurgitation – right ventricular function on cardiac MRI

Reference	**Park 2016[211]**
Study type and analysis	Prospective cohort study Multivariate/univariate Cox proportional hazards model (depending on prognostic factor) South Korea
Number of participants and characteristics	N=75 RV ejection fraction (RVEF) per 5% higher (continuous variable) on cardiac magnetic resonance (CMR) imaging, n=75 RVEF <46% on CMR, n=23 RVEF ≥46% on CMR, n=52 RV end-systolic volume index (RV-ESVI) per 10 ml/m^2 higher (continuous variable) on CMR, n=75 RV-ESVI ≥76 ml/m^2 on CMR, n=50 RV-ESVI <76 ml/m^2 on CMR, n=25 RV end-diastolic volume index (RV-EDVI) on CMR – continuous variable but increment used is unclear, n=75 Tricuspid regurgitation (TR) fraction on CMR – continuous variable but increment used is unclear, n=75 Severe isolated functional TR and underwent isolated TR surgery. Surgery performed by experienced surgeons with >100 cardiac surgeries annually for at least 5 years prior to the study. Of those included, 59 (78.7%) had tricuspid valve replacement and 16 (21.3%) had tricuspid annuloplasty with or without valvuloplasty. No concomitant procedures on other valves were performed at the time of the tricuspid procedures. **Inclusion criteria:** Severe functional TR (TR jet area >30% of right atrial area, inadequate coaptation of tricuspid valve leaflets and systolic flow reversal in hepatic veins).

Reference	Park 2016[211]
	Exclusion criteria: Haemodynamically significant primary TR based on imaging, surgical and pathological findings (TR occurring due to structural changes in the tricuspid valve leaflets and chordae as a result of several disease origins, such as rheumatic or degenerative valve disease or congenital, infections, traumatic or iatrogenic causes); coronary disease requiring intervention based on preoperative angiographic findings. **Values listed below are presented as mean (SD) or number (%)** • Age: 59.3 (8.9) years • Male/female: 14/61 (18.7%/81.3%) • Body mass index: 21.9 (2.9) kg/m^2 • Body surface area: 1.53 (0.15) m^2 • Systolic blood pressure: 119 (16) mmHg • Diastolic blood pressure: 67 (10) mmHg • NYHA class: ○ I, 2 (2.6%) ○ II, 32 (42.7%) ○ III, 36 (48.0%) ○ IV, 5 (6.7%) • Type of index TR surgery: ○ Tricuspid valve replacement, 59 (78.7%) ○ Tricuspid annuloplasty, 6 (8.0%) ○ Tricuspid annuloplasty + tricuspid valvuloplasty, 10 (13.3%) • Combined maze operation, 17 (22.7%) • Rhythm: ○ Sinus, 14 (18.7%) ○ Atrial fibrillation, 61 (81.3%) • Beta-blockers, 15 (20.0%) • Angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, 13 (17.3%) • Digoxin, 47 (62.7%)

Reference	Park 2016[211]
	- Loop diuretics, 44 (58.7%) - Spironolactone, 49 (65.3%) - Thiazide, 18 (24%) - Haemoglobin level: 12.3 (1.7) g/dL - Glomerular filtration rate: 64.6 (20.6) ml/min/1.73 m^2 - RV end-diastolic area on echo: 31 (7) mm^2 - RV end-systolic area on echo: 17 (5) mm^2 - RV fractional area change on echo: 46 (8)% - RV diameter on echo: 47 (7) mm - LV end-diastolic diameter on echo: 48 (6) mm^2 - LV end-systolic diameter on echo: 28 (11) mm^2 - LV ejection fraction on echo: 57 (8)% - TR fraction on echo: 35 (20)% - Median (IQR) TR fraction on echo: 39 (25-48)% - Pulmonary artery systolic pressure on echo: 39.6 (10.9) mmHg - RV-EDVI on CMR: 175 (61) ml/m^2 - RV-ESVI on CMR: 98 (46) ml/m^2 - RVEF on CMR: 48 (9)% - LV-EDVI on CMR: 95 (28) ml/m^2 - LV-ESVI on CMR: 45 (21) ml/m^2 - Cardiac index on CMR: 3.7 (1.1) l/min/m^2 - TR fraction on CMR: 46 (16)% - Median (IQR) TR fraction on CMR: 49 (33-60)% **Population source:** those matching inclusion criteria between April 2004 and April 2013 at a single centre.
Prognostic variable	RVEF per 5% higher (continuous variable) on CMR (continuous variable, no referent) RVEF <46% on CMR

Reference	**Park 2016**[211]
	RVEF ≥46% on CMR (referent) RV-ESVI per 10 ml/m^2 higher (continuous variable) on CMR (continuous variable, no referent) RV-ESVI ≥76 ml/m^2 on CMR RV-ESVI <76 ml/m^2 on CMR (referent) RV-EDVI on CMR – continuous variable but increment used is unclear (no referent) TR fraction on CMR – continuous variable but increment used is unclear (no referent) All patients underwent CMR within 1 month prior to surgery. Performed using 1.5T system using standard protocols. Same imaging unit used for all patients. Steady-state free-precession cine images obtained with breath hold to visualise ventricular wall motions. Entire short-axis images acquired at 6 mm interval with a 4 mm intersection gap from valve plane to apex to include whole ventricular volume. RV and LV end-diastolic volume and end-systolic volume, stroke volumes, cardiac output and ejection fractions were measured using software. Ventricular volumes and cardiac output were normalised for body surface area. TR amount was calculated by subtracting net pulmonary blood volume from RV stroke volume. TR fraction calculated by dividing TR amount by RV stroke volume. Analysis of cardiac MR images was performed by two experienced observers who were blinded to clinical data.
Confounders	Univariate/multivariate Cox proportional hazards model. Variables with univariate P-value <0.10 were incorporated into multivariate models. Factors included in adjusted analysis (applies for cardiac death and major postoperative cardiac events outcomes): • Continuous RVEF variable: age, sex, NYHA class, haemoglobin level and glomerular filtration rate • Threshold RVEF variable (<46%): unadjusted and estimated from Kaplan-Meier plots • Continuous RV-ESVI variable: age, sex, NYHA class, haemoglobin level and glomerular filtration rate • Threshold RV-ESVI variable (≥76%): unadjusted and estimated from Kaplan-Meier plots • Continuous RV-EDVI variable: unadjusted as only univariate results reported • Continuous TR fraction variable: unadjusted as only univariate results reported

Reference	Park 2016[211]
	For those that were adjusted (continuous RVEF variable and continuous RV-ESVI variable models), age was adjusted for in the model, which was the only confounder prespecified for postoperative mortality and unplanned hospital admission. Other listed prognostic variables were unadjusted only and therefore had not adjusted for age.
Outcomes and effect sizes	**Cardiac death following TR surgery** RVEF on CMR **HR 0.714 (95% CI 0.528 to 0.966, P=0.029) for RVEF per 5% higher (analysed as a continuous variable) on CMR** – adjusted for age, sex, NYHA class, haemoglobin level and glomerular filtration rate **HR 5.06 (95% CI 1.56 to 16.46, P=0.007) for RVEF <46% vs. RVEF ≥46% on CMR** – unadjusted, estimated from data provided RV-ESVI on CMR **HR 1.183 (95% CI 1.025 to 1.365, P=0.021) for RV-ESVI per 10 ml/m^2 higher (analysed as a continuous variable) on CMR**– adjusted for age, sex, NYHA class, haemoglobin level and glomerular filtration rate **HR 0.29 (95% CI 0.09 to 0.91, P=0.034) for RV-ESVI ≥76 ml/m^2 vs. RV-ESVI <76 ml/m^2 on CMR** – unadjusted, estimated from data provided RV-EDVI on CMR **HR 1.008 (95% CI 0.999 to 1.017, P=0.076) for RV-EDVI on CMR as a continuous variable (increment unclear)** – unadjusted TR fraction on CMR **HR 0.985 (95% CI 0.953 to 1.019, P=0.395) for TR fraction on CMR as a continuous variable (increment unclear)** – unadjusted **Major postoperative cardiac events (cardiac death or unplanned cardiac-related readmission) following TR surgery** RVEF on CMR **HR 0.795 (95% CI 0.649 to 0.974, P=0.027) for RVEF per 5% higher (analysed as a continuous variable) on CMR** – adjusted for age, sex, NYHA class, haemoglobin level and glomerular filtration rate **HR 3.94 (95% CI 1.59 to 9.76, P=0.003) for RVEF <46% vs. RVEF ≥46% on CMR** – unadjusted, estimated from data provided

Reference	Park 2016[211]
	RV-ESVI on CMR **HR 1.102 (95% CI 0.997 to 1.218, P=0.057) for RV-ESVI per 10 ml/m^2 higher (analysed as a continuous variable) on CMR** – adjusted for age, sex, NYHA class, haemoglobin level and glomerular filtration rate **HR 0.46 (95% CI 0.19 to 1.11, P=0.029) for RV-ESVI ≥76 ml/m^2 vs. RV-ESVI <76 ml/m^2 on CMR** – unadjusted, estimated from data provided RV-EDVI on CMR **HR 1.005 (95% CI 0.998 to 1.012, P=0.163) for RV-EDVI on CMR as a continuous variable (increment unclear)** – unadjusted TR fraction on CMR **HR 0.986 (95% CI 0.960 to 1.013, P=0.293) for TR fraction on CMR as a continuous variable (increment unclear)** – unadjusted During follow-up, 13 patients died due to cardiac reasons (n=8 due to heart failure, n=1 due to infective endocarditis, n=1 due to ventricular fibrillation and n=3 were sudden cardiac deaths). There were a further 7 non-cardiac deaths (n=3 due to pneumonia, n=1 due to mediastinitis, n=1 due to intracranial haemorrhage, n=1 due to renal failure and n=1 due to malignancy). Of the 55 patients that did not die, n=6 and n=8 experienced unplanned readmission for cardiovascular problems within 1 year and 5 years, respectively. The 5-year survival and 5-year event-free survival rates were 76.0% (57/75) and 65.3% (49/75), respectively. Cardiac deaths occurred in 8/23 (34.8%) of those with RVEF on CMR <46% and in 5/52 (9.6%) of those with RVEF on CMR ≥46%. Major postoperative cardiac events occurred in 12/23 (52.2%) of those with RVEF <46% and in 10/52 (19.2%) of those with RVEF ≥46%. Follow-up was performed by clinical visits, medical record review and telephone contact and was complete in 100% of patients. All medical records reviewed by independent research nurse and telephone interviews arranged if needed to monitor development of clinical events. Institutional database was matched to nationwide official data on death certification provided by National Statistical Office to validate accuracy of mortality information. Primary endpoint was cardiac death. All-cause mortality and unplanned readmission due to cardiovascular problems at follow-up were also collected. Composite outcome of major postoperative cardiac events was defined as cardiac death or unplanned cardiac-related readmission. Median (IQR) follow-up following surgery: 57 (21-82) months
Comments	**Cardiac death following TR surgery**

Reference	Park 2016[211]
	<u>RVEF on CMR – continuous, adjusted variable</u> Risk of bias: 1. Study participation LOW 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement HIGH 5. Study confounding LOW 6. Statistical analysis HIGH 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH Indirectness: • Population – all underwent intervention for severe functional TR so does not represent population where there is uncertainty about whether there is an indication for intervention. • Outcome – only includes cardiac deaths in the analysis rather than any mortality <u>RVEF on CMR – threshold (<46% vs. ≥46%), unadjusted variable</u> Risk of bias: 1. Study participation LOW 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement HIGH 5. Study confounding VERY HIGH 6. Statistical analysis HIGH 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH Indirectness: • Population – all underwent intervention for severe functional TR so does not represent population where there is uncertainty about whether there is an indication for intervention. • Outcome – only includes cardiac deaths in the analysis rather than any mortality

Reference	**Park 2016[211]**
	• Confounding – no adjustment for age, which was the prespecified confounder for postoperative mortality. Downgraded for this as part of risk of bias rating, so not downgraded further for indirectness. <u>RV-ESVI on CMR – continuous, adjusted variable</u> Risk of bias: 1. Study participation LOW 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement HIGH 5. Study confounding LOW 6. Statistical analysis HIGH 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH Indirectness: • Population – all underwent intervention for severe functional TR so does not represent population where there is uncertainty about whether there is an indication for intervention. • Outcome – only includes cardiac deaths in the analysis rather than any mortality <u>RV-ESVI on CMR – threshold (≥76 ml/m^2 vs <76 ml/m^2), unadjusted variable</u> Risk of bias: 1. Study participation LOW 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement HIGH 5. Study confounding VERY HIGH 6. Statistical analysis HIGH 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH Indirectness:

Reference	**Park 2016[211]**
	• Population – all underwent intervention for severe functional TR so does not represent population where there is uncertainty about whether there is an indication for intervention. • Outcome – only includes cardiac deaths in the analysis rather than any mortality • Confounding – no adjustment for age, which was the prespecified confounder for postoperative mortality. Downgraded for this as part of risk of bias rating, so not downgraded further for indirectness. RV-EDVI on CMR – continuous, unadjusted variable Risk of bias: 1. Study participation LOW 2. Study attrition LOW 3. Prognostic factor measurement HIGH 4. Outcome Measurement HIGH 5. Study confounding VERY HIGH 6. Statistical analysis LOW 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH Indirectness: • Population – all underwent intervention for severe functional TR so does not represent population where there is uncertainty about whether there is an indication for intervention. • Outcome – only includes cardiac deaths in the analysis rather than any mortality • Confounding – no adjustment for age, which was the prespecified confounder for postoperative mortality. Downgraded for this as part of risk of bias rating, so not downgraded further for indirectness. TR fraction on CMR – continuous, unadjusted variable Risk of bias: 1. Study participation LOW 2. Study attrition LOW 3. Prognostic factor measurement HIGH 4. Outcome Measurement HIGH 5. Study confounding VERY HIGH

Reference	Park 2016[211]
	6. Statistical analysis LOW 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH Indirectness: • Population – all underwent intervention for severe functional TR so does not represent population where there is uncertainty about whether there is an indication for intervention. • Prognostic factor – effective regurgitant orifice area listed in protocol and TR fraction is not the same as this. • Outcome – only includes cardiac deaths in the analysis rather than any mortality • Confounding – no adjustment for age, which was the prespecified confounder for postoperative mortality. Downgraded for this as part of risk of bias rating, so not downgraded further for indirectness. **Major postoperative cardiac events (cardiac death or unplanned cardiac-related readmission) following TR surgery** RVEF on CMR – continuous, adjusted variable Risk of bias: 1. Study participation LOW 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement HIGH 5. Study confounding LOW 6. Statistical analysis HIGH 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH Indirectness: • Population – all underwent intervention for severe functional TR so does not represent population where there is uncertainty about whether there is an indication for intervention. • Outcome – only includes cardiac deaths in the analysis rather than any mortality and is a composite of two outcomes listed in the protocol rather than reporting data for each separately. RVEF on CMR – threshold (<46% vs. ≥46%), unadjusted variable Risk of bias:

Reference	Park 2016[211]
	1. Study participation LOW 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement HIGH 5. Study confounding VERY HIGH 6. Statistical analysis HIGH 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH Indirectness: • Population – all underwent intervention for severe functional TR so does not represent population where there is uncertainty about whether there is an indication for intervention. • Outcome – only includes cardiac deaths in the analysis rather than any mortality and is a composite of two outcomes listed in the protocol rather than reporting data for each separately. • Confounding – no adjustment for age, which was the prespecified confounder for postoperative mortality and readmission for cardiac reasons. Downgraded for this as part of risk of bias rating, so not downgraded further for indirectness. RV-ESVI on CMR – continuous, adjusted variable Risk of bias: 1. Study participation LOW 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement HIGH 5. Study confounding LOW 6. Statistical analysis HIGH 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH Indirectness: • Population – all underwent intervention for severe functional TR so does not represent population where there is uncertainty about whether there is an indication for intervention.

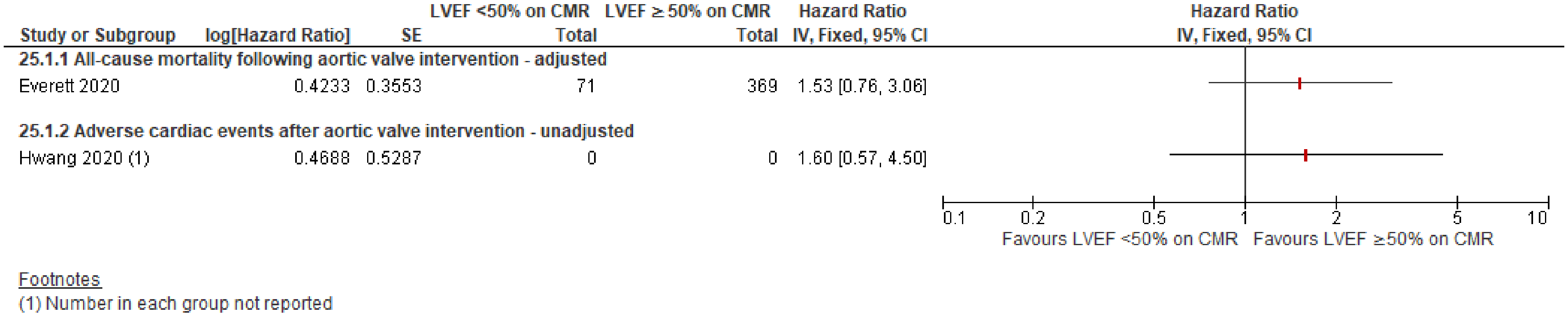
Reference	Park 2016[211]
	- Outcome – only includes cardiac deaths in the analysis rather than any mortality and is a composite of two outcomes listed in the protocol rather than reporting data for each separately. <u>RV-ESVI on CMR – threshold (≥76 ml/m^2 vs <76 ml/m^2), unadjusted variable</u> Risk of bias: 1. Study participation LOW 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement HIGH 5. Study confounding VERY HIGH 6. Statistical analysis HIGH 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH Indirectness: - Population – all underwent intervention for severe functional TR so does not represent population where there is uncertainty about whether there is an indication for intervention. - Outcome – only includes cardiac deaths in the analysis rather than any mortality and is a composite of two outcomes listed in the protocol rather than reporting data for each separately. - Confounding – no adjustment for age, which was the prespecified confounder for postoperative mortality and readmission for cardiac reasons. Downgraded for this as part of risk of bias rating, so not downgraded further for indirectness. <u>RV-EDVI on CMR – continuous, unadjusted variable</u> Risk of bias: 1. Study participation LOW 2. Study attrition LOW 3. Prognostic factor measurement HIGH 4. Outcome Measurement HIGH 5. Study confounding VERY HIGH 6. Statistical analysis LOW 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH

Reference	**Park 2016**[211]
	Indirectness: - Population – all underwent intervention for severe functional TR so does not represent population where there is uncertainty about whether there is an indication for intervention. - Outcome – only includes cardiac deaths in the analysis rather than any mortality and is a composite of two outcomes listed in the protocol rather than reporting data for each separately. - Confounding – no adjustment for age, which was the prespecified confounder for postoperative mortality and readmission for cardiac reasons. Downgraded for this as part of risk of bias rating, so not downgraded further for indirectness. <u>TR fraction on CMR – continuous, unadjusted variable</u> Risk of bias: 1. Study participation LOW 2. Study attrition LOW 3. Prognostic factor measurement HIGH 4. Outcome Measurement HIGH 5. Study confounding VERY HIGH 6. Statistical analysis LOW 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH Indirectness: - Population – all underwent intervention for severe functional TR so does not represent population where there is uncertainty about whether there is an indication for intervention. - Prognostic factor – effective regurgitant orifice area listed in protocol and TR fraction is not the same as this. - Outcome – only includes cardiac deaths in the analysis rather than any mortality and is a composite of two outcomes listed in the protocol rather than reporting data for each separately. - Confounding – no adjustment for age, which was the prespecified confounder for postoperative mortality and readmission for cardiac reasons. Downgraded for this as part of risk of bias rating, so not downgraded further for indirectness.

Appendix E – Forest plots

E.1 Aortic stenosis – left ventricular ejection fraction (LVEF) on cardiac MRI

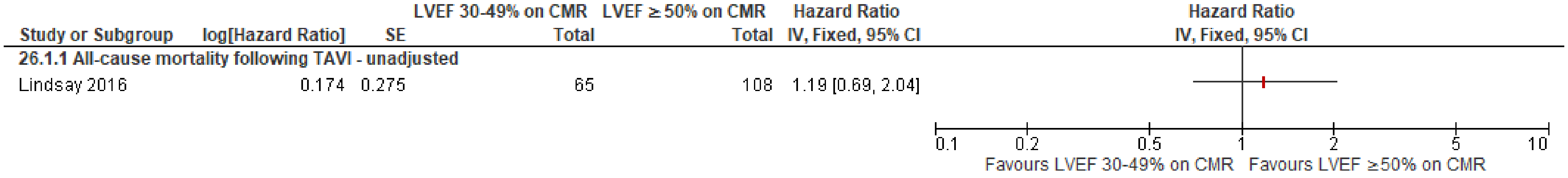
Figure 2: LVEF <50% compared to ≥50% on cardiac MRI in severe AS scheduled for AVR



Study or Subgroup	log[Hazard Ratio]	SE	LVEF <50% on CMR Total	LVEF ≥ 50% on CMR Total	Hazard Ratio IV, Fixed, 95% CI
25.1.1 All-cause mortality following aortic valve intervention - adjusted					
Everett 2020	0.4233	0.3553	71	369	1.53 [0.76, 3.06]
25.1.2 Adverse cardiac events after aortic valve intervention - unadjusted					
Hwang 2020 (1)	0.4688	0.5287	0	0	1.60 [0.57, 4.50]

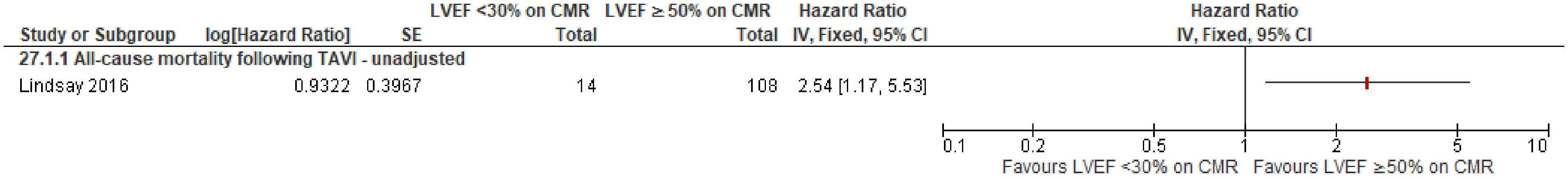
Footnotes
(1) Number in each group not reported

Figure 3: LVEF 30-49% compared to ≥50% on cardiac MRI in those undergoing TAVI for AS (>70% with symptoms at rest or marked limitation of physical activity and median aortic valve area on echocardiography 0.60 cm^2 in whole cohort, though unclear for those included in this analysis)



Study or Subgroup	log[Hazard Ratio]	SE	LVEF 30-49% on CMR Total	LVEF ≥ 50% on CMR Total	Hazard Ratio IV, Fixed, 95% CI
26.1.1 All-cause mortality following TAVI - unadjusted					
Lindsay 2016	0.174	0.275	65	108	1.19 [0.69, 2.04]

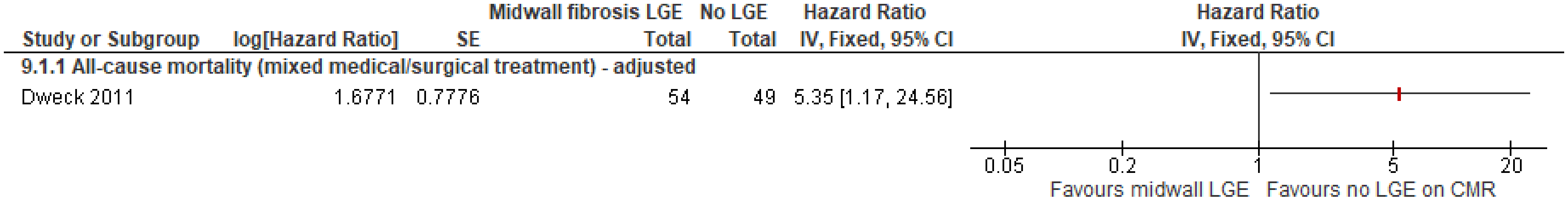
Figure 4: LVEF <30% compared to ≥50% on cardiac MRI in those undergoing TAVI for AS (>70% with symptoms at rest or marked limitation of physical activity and median aortic valve area on echocardiography 0.60 cm^2 in whole cohort, though unclear for those included in this analysis)



Study or Subgroup	log[Hazard Ratio]	SE	LVEF <30% on CMR Total	LVEF ≥ 50% on CMR Total	Hazard Ratio IV, Fixed, 95% CI
27.1.1 All-cause mortality following TAVI - unadjusted					
Lindsay 2016	0.9322	0.3967	14	108	2.54 [1.17, 5.53]

E.2 Aortic stenosis – myocardial fibrosis on cardiac MRI

Figure 5: Midwall fibrosis LGE pattern compared to no LGE on cardiac MRI in moderate or severe AS (symptomatic status unclear)



Study or Subgroup	log[Hazard Ratio]	SE	Midwall fibrosis LGE Total	No LGE Total	Hazard Ratio IV, Fixed, 95% CI
9.1.1 All-cause mortality (mixed medical/surgical treatment) - adjusted					
Dweck 2011	1.6771	0.7776	54	49	5.35 [1.17, 24.56]

Figure 6: Infarct fibrosis LGE pattern compared to no LGE on cardiac MRI in moderate or severe AS (symptomatic status unclear)

Study or Subgroup	log[Hazard Ratio]	SE	Infarct fibrosis LGE Total	No LGE Total	Hazard Ratio IV, Fixed, 95% CI
10.1.1 All-cause mortality (mixed medical/surgical treatment) - adjusted					
Dweck 2011	0.94	0.8538	40	49	2.56 [0.48, 13.65]

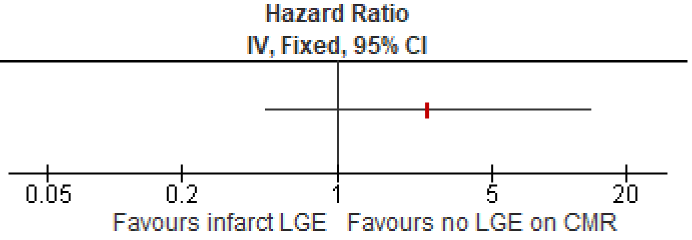
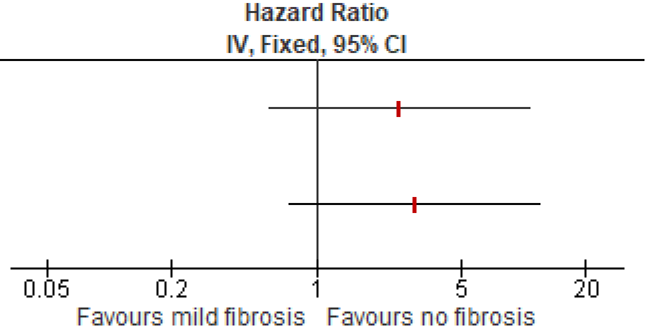


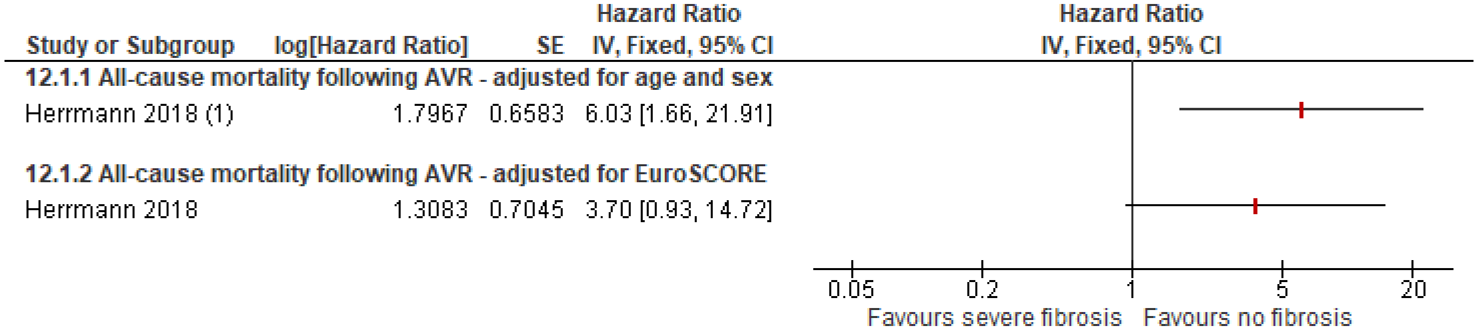
Figure 7: Mild fibrosis compared to no fibrosis on cardiac MRI in symptomatic severe AS referred for AVR

Study or Subgroup	log[Hazard Ratio]	SE	Hazard Ratio IV, Fixed, 95% CI
11.1.1 All-cause mortality following AVR - adjusted for age and sex			
Herrmann 2018 (1)	0.9243	0.7359	2.52 [0.60, 10.66]
11.1.2 All-cause mortality following AVR - adjusted for EuroSCORE			
Herrmann 2018	1.0919	0.709	2.98 [0.74, 11.96]



Footnotes
(1) Number in each group not reported

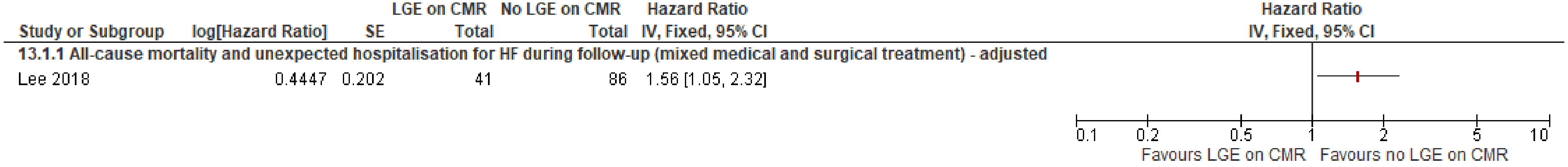
Figure 8: Severe fibrosis compared to no fibrosis on cardiac MRI in symptomatic severe AS referred for AVR



Study or Subgroup	log[Hazard Ratio]	SE	Hazard Ratio IV, Fixed, 95% CI
12.1.1 All-cause mortality following AVR - adjusted for age and sex			
Herrmann 2018 (1)	1.7967	0.6583	6.03 [1.66, 21.91]
12.1.2 All-cause mortality following AVR - adjusted for EuroSCORE			
Herrmann 2018	1.3083	0.7045	3.70 [0.93, 14.72]

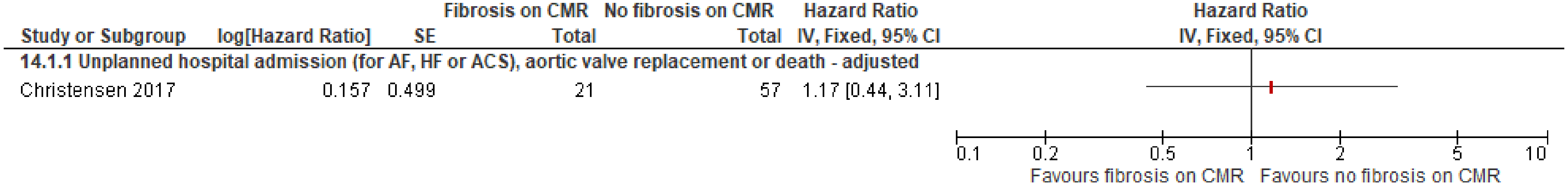
Footnotes
(1) Number in each group not reported

Figure 9: LGE compared to no LGE on cardiac MRI in moderate or severe AS (proportion with severe AS was 62.2% and with any typical AS symptoms was 54.5%)



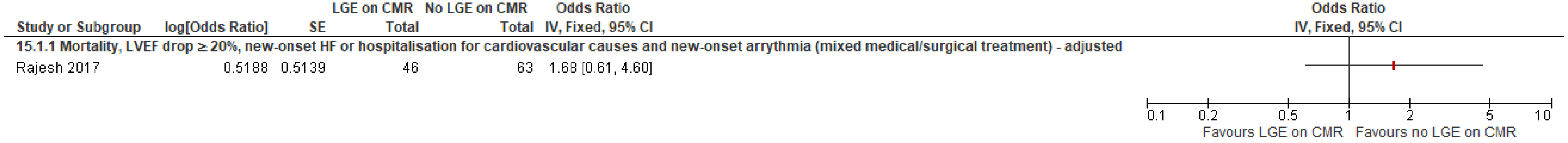
Study or Subgroup	log[Hazard Ratio]	SE	LGE on CMR Total	No LGE on CMR Total	Hazard Ratio IV, Fixed, 95% CI
13.1.1 All-cause mortality and unexpected hospitalisation for HF during follow-up (mixed medical and surgical treatment) - adjusted					
Lee 2018	0.4447	0.202	41	86	1.56 [1.05, 2.32]

Figure 10: Fibrosis compared to no fibrosis on cardiac MRI in asymptomatic severe AS



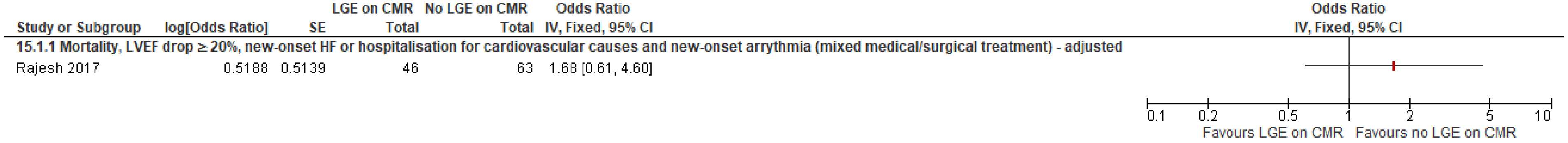
Study or Subgroup	log[Hazard Ratio]	SE	Fibrosis on CMR Total	No fibrosis on CMR Total	Hazard Ratio IV, Fixed, 95% CI
14.1.1 Unplanned hospital admission (for AF, HF or ACS), aortic valve replacement or death - adjusted					
Christensen 2017	0.157	0.499	21	57	1.17 [0.44, 3.11]

Figure 11: LGE compared to no LGE on cardiac MRI in severe AS with/without symptoms (16.5% were in NYHA class III/IV)



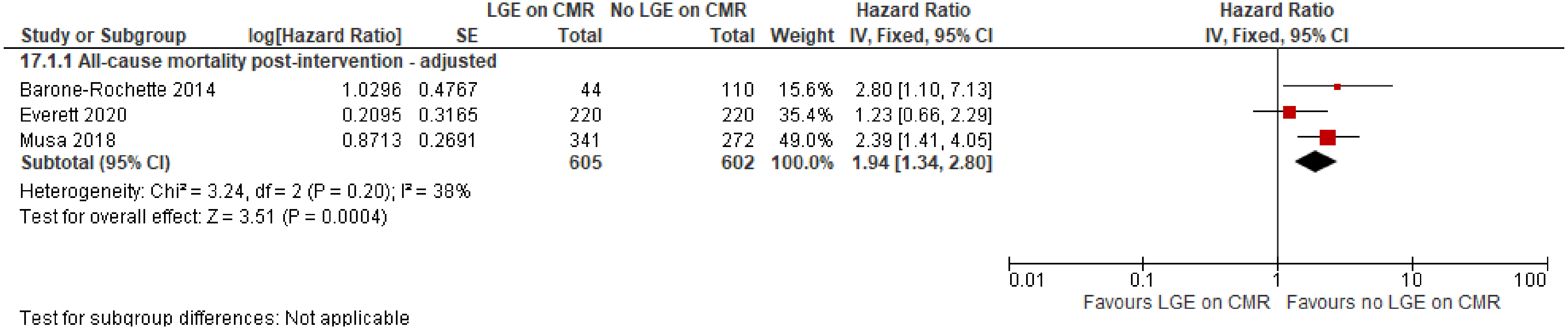
Study or Subgroup	log[Odds Ratio]	SE	LGE on CMR Total	No LGE on CMR Total	Odds Ratio IV, Fixed, 95% CI
15.1.1 Mortality, LVEF drop ≥ 20%, new-onset HF or hospitalisation for cardiovascular causes and new-onset arrythmia (mixed medical/surgical treatment) - adjusted					
Rajesh 2017	0.5188	0.5139	46	63	1.68 [0.61, 4.60]

Figure 12: LGE (myocardial fibrosis) compared to no LGE on cardiac MRI in severe AS undergoing AVR (28.8% with NYHA class ≥III)



Study or Subgroup	log[Odds Ratio]	SE	LGE on CMR Total	No LGE on CMR Total	Odds Ratio IV, Fixed, 95% CI
15.1.1 Mortality, LVEF drop ≥ 20%, new-onset HF or hospitalisation for cardiovascular causes and new-onset arrythmia (mixed medical/surgical treatment) - adjusted					
Rajesh 2017	0.5188	0.5139	46	63	1.68 [0.61, 4.60]

Figure 13: LGE (myocardial fibrosis) compared to no LGE on cardiac MRI in severe AS undergoing AVR (proportion with NYHA class ≥III differed between studies but was similar – 36%, 40.1% and 27%)



Study or Subgroup	log[Hazard Ratio]	SE	LGE on CMR Total	No LGE on CMR Total	Weight	Hazard Ratio IV, Fixed, 95% CI
17.1.1 All-cause mortality post-intervention - adjusted						
Barone-Rochette 2014	1.0296	0.4767	44	110	15.6%	2.80 [1.10, 7.13]
Everett 2020	0.2095	0.3165	220	220	35.4%	1.23 [0.66, 2.29]
Musa 2018	0.8713	0.2691	341	272	49.0%	2.39 [1.41, 4.05]
Subtotal (95% CI)			**605**	**602**	**100.0%**	**1.94 [1.34, 2.80]**

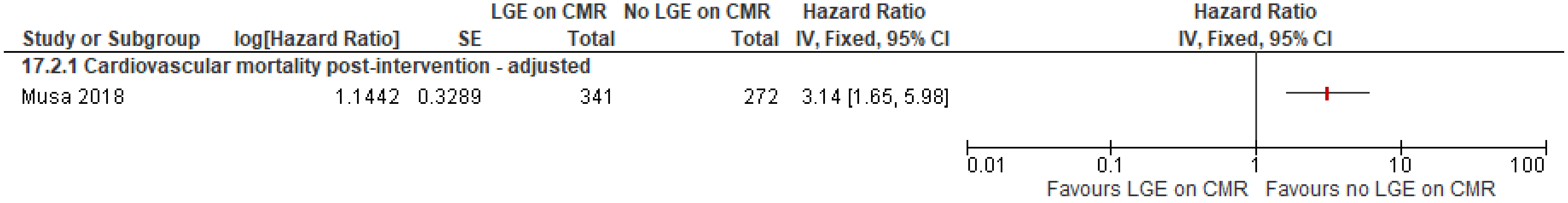
Heterogeneity: Chi² = 3.24, df = 2 (P = 0.20); I² = 38%

Test for overall effect: Z = 3.51 (P = 0.0004)

Test for subgroup differences: Not applicable

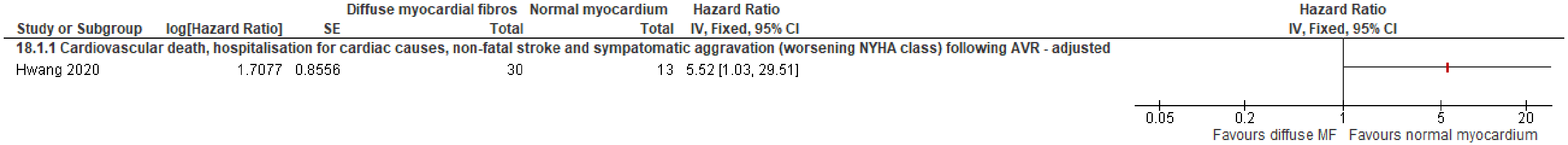
Barone-Rochette 2014 was adjusted for NYHA class III/IV and left bundle branch block, Everett 2020 was adjusted for extracellular volume percentage, age, gender, LVEF <50% and peak aortic jet velocity and Musa 2018 was adjusted for RV ejection fraction on cardiac MRI, LVEF on cardiac MRI, indexed atrial volume on cardiac MRI, atrial fibrillation, LV maximal wall thickness, STS score, LV stroke volume score on cardiac MRI, coronary artery disease, aortic valve area on echocardiography and age. Though Barone-Rochette 2014 had not accounted for the key confounder of age, age was very similar between the two prognostic groups in this study and was therefore included in the pooled analysis.

Figure 14: LGE (myocardial fibrosis) compared to no LGE on cardiac MRI in severe AS undergoing AVR (proportion with NYHA class ≥III was 40.1%)



Study or Subgroup	log[Hazard Ratio]	SE	LGE on CMR Total	No LGE on CMR Total	Hazard Ratio IV, Fixed, 95% CI
17.2.1 Cardiovascular mortality post-intervention - adjusted					
Musa 2018	1.1442	0.3289	341	272	3.14 [1.65, 5.98]

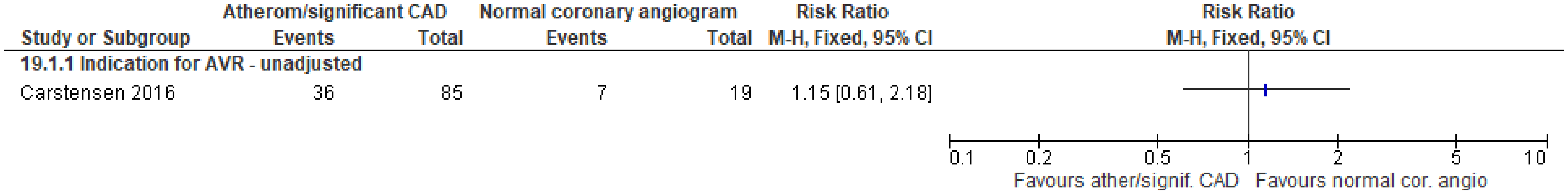
Figure 15: Diffuse myocardial fibrosis compared to normal myocardium on cardiac MRI in severe AS scheduled for AVR (mean NYHA class 2.1)



Study or Subgroup	log[Hazard Ratio]	SE	Diffuse myocardial fibros Total	Normal myocardium Total	Hazard Ratio IV, Fixed, 95% CI
18.1.1 Cardiovascular death, hospitalisation for cardiac causes, non-fatal stroke and sympatomatic aggravation (worsening NYHA class) following AVR - adjusted					
Hwang 2020	1.7077	0.8556	30	13	5.52 [1.03, 29.51]

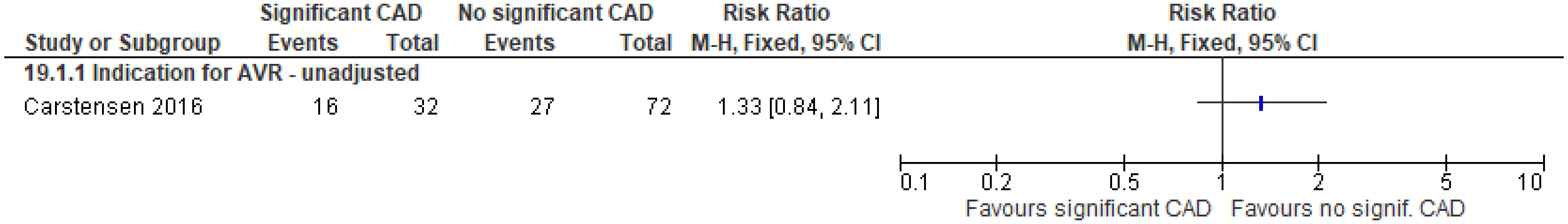
E.3 Aortic stenosis – coronary artery disease on CT

Figure 16: Significant stenosis (>50% luminal diameter) of 1, 2 or 3 vessels or atheromatosis compared to normal coronary angiogram on CT in asymptomatic moderate-severe AS



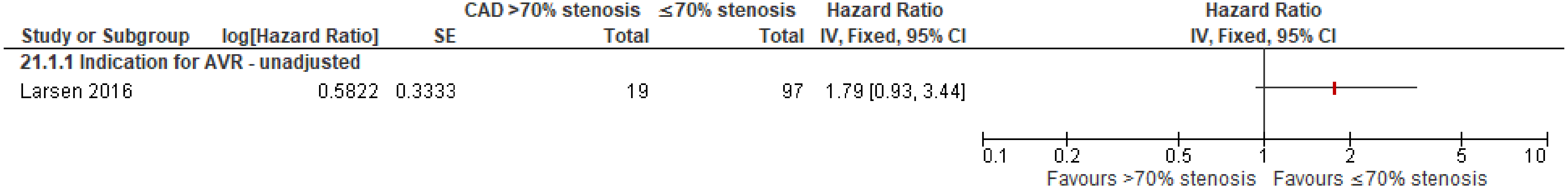
Study or Subgroup	Atherom/significant CAD Events	Atherom/significant CAD Total	Normal coronary angiogram Events	Normal coronary angiogram Total	Risk Ratio M-H, Fixed, 95% CI
19.1.1 Indication for AVR - unadjusted					
Carstensen 2016	36	85	7	19	1.15 [0.61, 2.18]

Figure 17: Significant stenosis (>50% luminal diameter) of 1, 2 or 3 vessels compared to normal coronary angiogram or atheromatosis on CT in asymptomatic moderate-severe AS



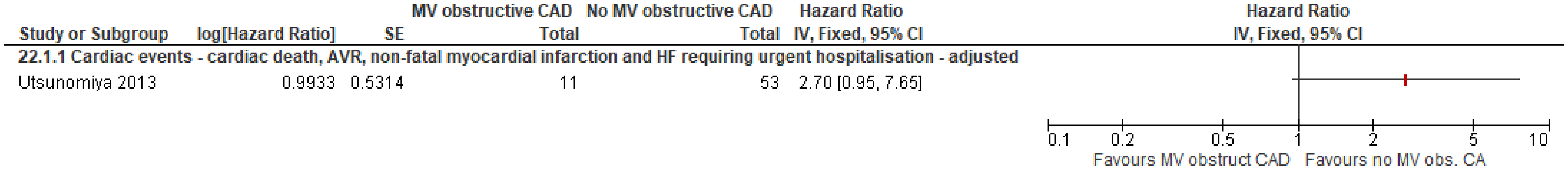
Study or Subgroup	Significant CAD Events	Significant CAD Total	No significant CAD Events	No significant CAD Total	Risk Ratio M-H, Fixed, 95% CI
19.1.1 Indication for AVR - unadjusted					
Carstensen 2016	16	32	27	72	1.33 [0.84, 2.11]

Figure 18: Coronary artery disease >70% stenosis compared to ≤70% stenosis on CT in asymptomatic mild-severe AS (mean aortic valve area on echocardiography was 1.01 cm^2)



Study or Subgroup	log[Hazard Ratio]	SE	CAD >70% stenosis Total	≤70% stenosis Total	Hazard Ratio IV, Fixed, 95% CI
21.1.1 Indication for AVR - unadjusted					
Larsen 2016	0.5822	0.3333	19	97	1.79 [0.93, 3.44]

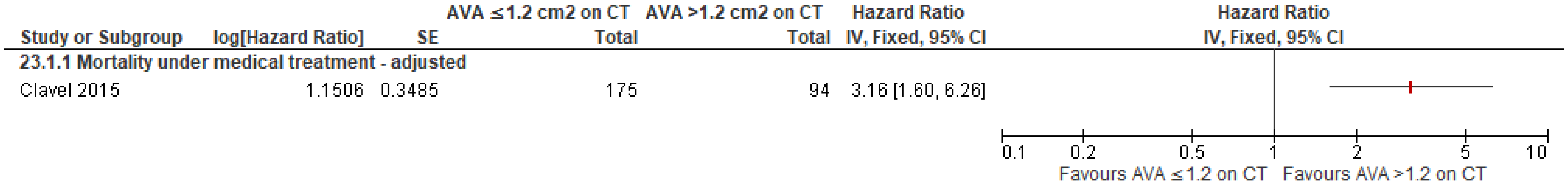
Figure 19: Multivessel obstructive coronary artery disease compared to no multivessel coronary artery disease on CT in asymptomatic mild-severe AS (with 45% being severe cases)



Study or Subgroup	log[Hazard Ratio]	SE	MV obstructive CAD Total	No MV obstructive CAD Total	Hazard Ratio IV, Fixed, 95% CI
22.1.1 Cardiac events - cardiac death, AVR, non-fatal myocardial infarction and HF requiring urgent hospitalisation - adjusted					
Utsunomiya 2013	0.9933	0.5314	11	53	2.70 [0.95, 7.65]

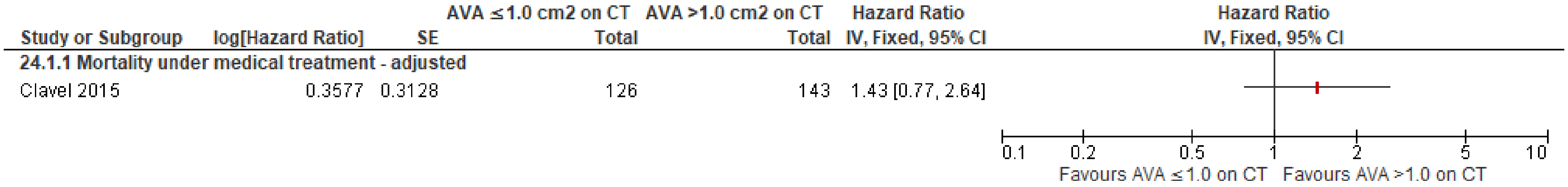
E.4 Aortic stenosis – aortic valve area on CT

Figure 20: Aortic valve area ≤1.2 cm^2 compared to >1.2 cm^2 on CT in AS patients undergoing CT and echocardiography in same episode of care (45% with NYHA class III/IV, mean aortic valve area 0.94 cm^2)



			AVA ≤1.2 cm2 on CT	AVA >1.2 cm2 on CT	Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Total	Total	IV, Fixed, 95% CI
23.1.1 Mortality under medical treatment - adjusted					
Clavel 2015	1.1506	0.3485	175	94	3.16 [1.60, 6.26]

Figure 21: Aortic valve area ≤1.2 cm^2 compared to >1.2 cm^2 on CT in AS patients undergoing CT and echocardiography in same episode of care (45% with NYHA class III/IV, mean aortic valve area 0.94 cm^2)



			AVA ≤1.0 cm2 on CT	AVA >1.0 cm2 on CT	Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Total	Total	IV, Fixed, 95% CI
24.1.1 Mortality under medical treatment - adjusted					
Clavel 2015	0.3577	0.3128	126	143	1.43 [0.77, 2.64]

E.5 Aortic stenosis – aortic valve calcium score on CT

Figure 22: Severe aortic valve calcification (≥2065 in AU in men and ≥1274 AU in women) compared to non-severe aortic valve calcification (<2065 AU in men and <1274 AU in women) on CT in at least mild AS under conservative management (27% with heart failure symptoms and mean gradient 35 mmHg)

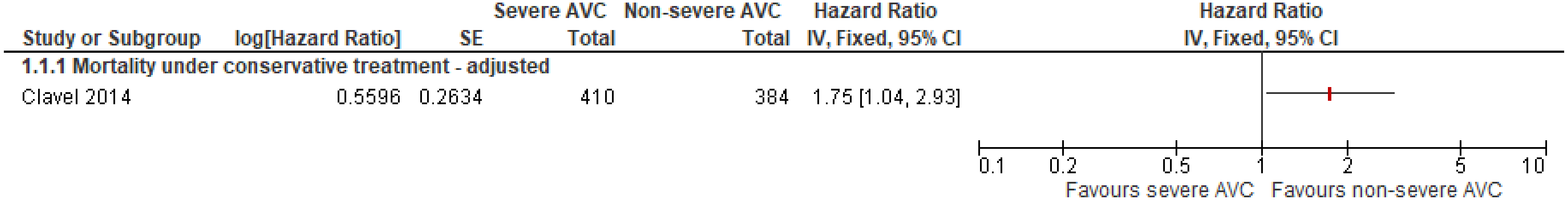
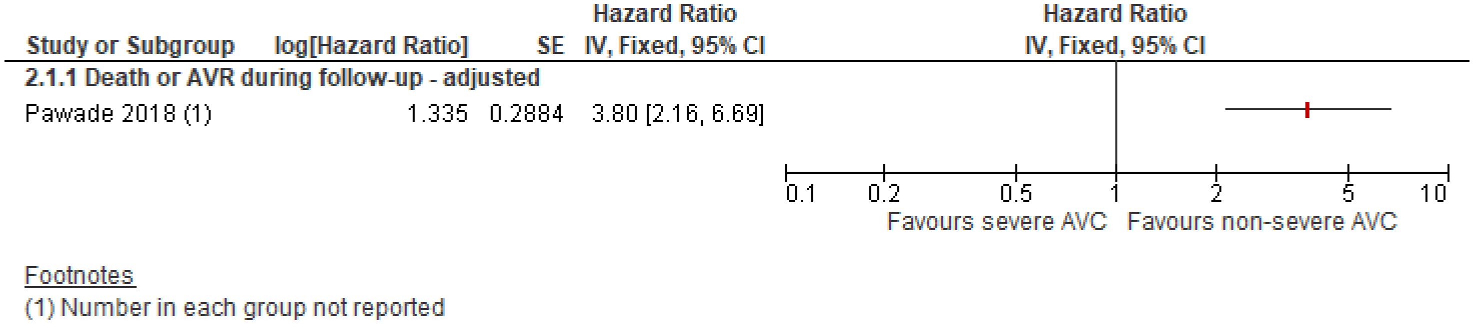
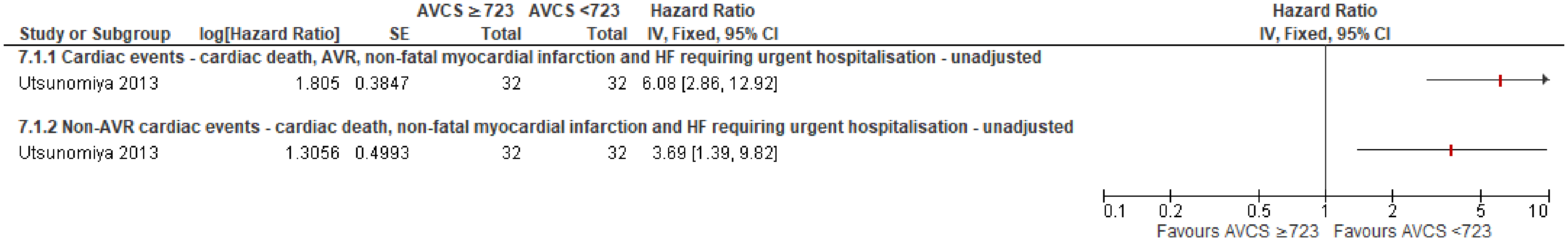


Figure 23: Severe aortic valve calcium (≥2065 AU for men and ≥1274 AU for women) compared to non-severe AVC (<2065 AU for men and <1274 AU for women) on CT in various AS presentations, including mild-severe with symptom status varying between patients (only includes those where decision on whether to perform an intervention had not been made prior to CT in outcome analysis)



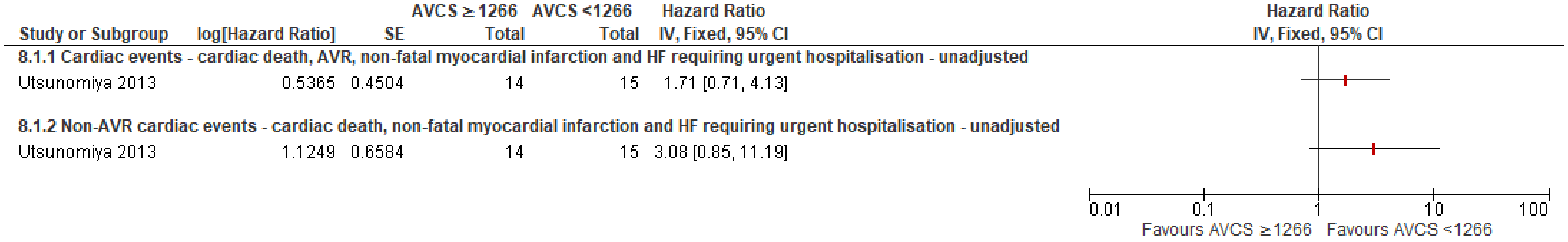
Footnotes
(1) Number in each group not reported

Figure 24: Aortic valve calcium score ≥723 compared to <723 on CT in asymptomatic mild-severe AS (with 45% being severe cases)



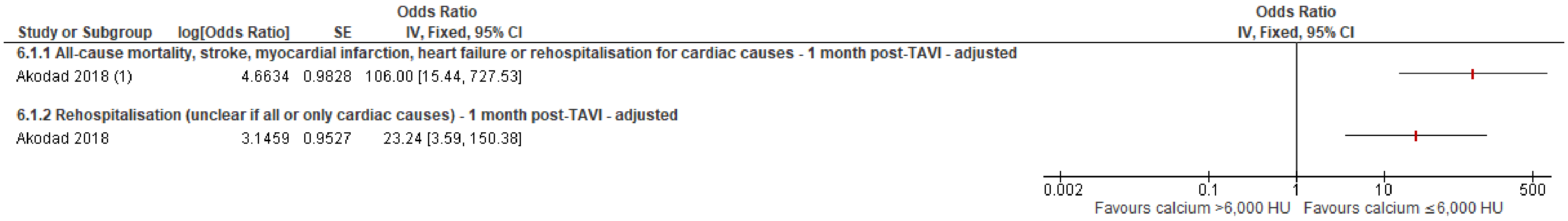
Study or Subgroup	log[Hazard Ratio]	SE	AVCS ≥ 723 Total	AVCS <723 Total	Hazard Ratio IV, Fixed, 95% CI
7.1.1 Cardiac events - cardiac death, AVR, non-fatal myocardial infarction and HF requiring urgent hospitalisation - unadjusted					
Utsunomiya 2013	1.805	0.3847	32	32	6.08 [2.86, 12.92]
7.1.2 Non-AVR cardiac events - cardiac death, non-fatal myocardial infarction and HF requiring urgent hospitalisation - unadjusted					
Utsunomiya 2013	1.3056	0.4993	32	32	3.69 [1.39, 9.82]

Figure 25: Aortic valve calcium score ≥1266 compared to <1266 on CT in asymptomatic severe AS subgroup



Study or Subgroup	log[Hazard Ratio]	SE	AVCS ≥ 1266 Total	AVCS <1266 Total	Hazard Ratio IV, Fixed, 95% CI
8.1.1 Cardiac events - cardiac death, AVR, non-fatal myocardial infarction and HF requiring urgent hospitalisation - unadjusted					
Utsunomiya 2013	0.5365	0.4504	14	15	1.71 [0.71, 4.13]
8.1.2 Non-AVR cardiac events - cardiac death, non-fatal myocardial infarction and HF requiring urgent hospitalisation - unadjusted					
Utsunomiya 2013	1.1249	0.6584	14	15	3.08 [0.85, 11.19]

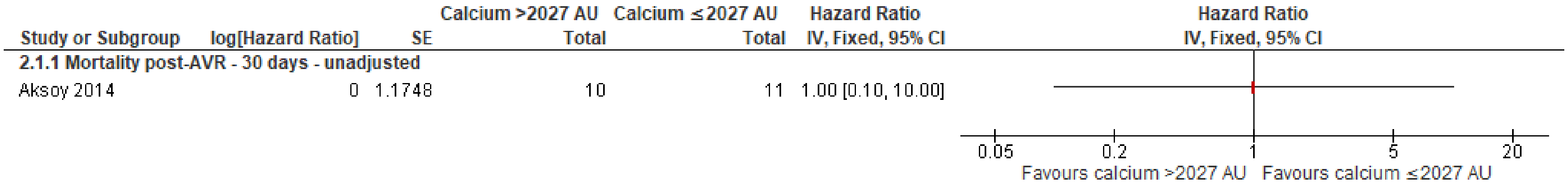
Figure 26: Calcium score >6,000 HU vs. ≤6,000 HU on CT in undergoing those undergoing TAVI for AS (>50% NYHA class ≥3 and mean gradient consistent with severe AS)



Study or Subgroup	log[Odds Ratio]	SE	Odds Ratio IV, Fixed, 95% CI
6.1.1 All-cause mortality, stroke, myocardial infarction, heart failure or rehospitalisation for cardiac causes - 1 month post-TAVI - adjusted			
Akodad 2018 (1)	4.6634	0.9828	106.00 [15.44, 727.53]
6.1.2 Rehospitalisation (unclear if all or only cardiac causes) - 1 month post-TAVI - adjusted			
Akodad 2018	3.1459	0.9527	23.24 [3.59, 150.38]

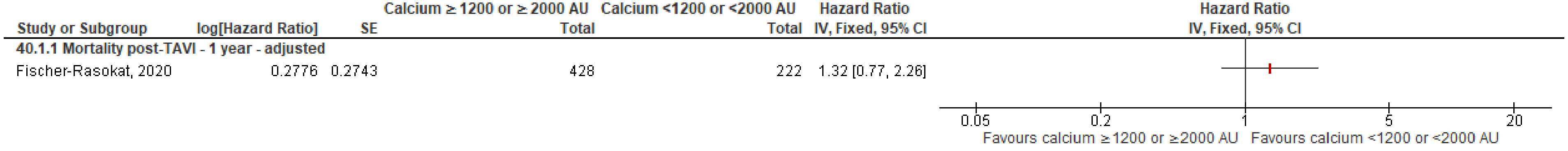
Footnotes
(1) Number in each group not reported

Figure 27: Calcium score >2027 compared to ≤2027 AU on CT in low-flow low-gradient severe AS undergoing surgical AVR



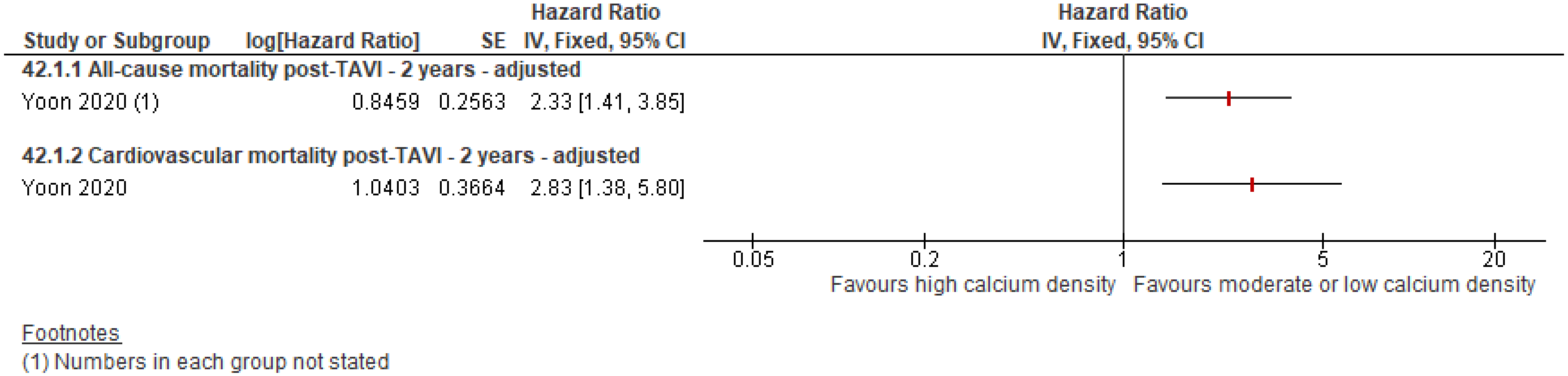
Study or Subgroup	log[Hazard Ratio]	SE	Calcium >2027 AU Total	Calcium ≤2027 AU Total	Hazard Ratio IV, Fixed, 95% CI
2.1.1 Mortality post-AVR - 30 days - unadjusted					
Aksoy 2014	0	1.1748	10	11	1.00 [0.10, 10.00]

Figure 28: Aortic valve calcium score ≥1200 in women and ≥2000 AU in men compared to <1200 and <2000 on CT in low-gradient severe AS undergoing TAVI



Study or Subgroup	log[Hazard Ratio]	SE	Calcium ≥ 1200 or ≥ 2000 AU Total	Calcium <1200 or <2000 AU Total	Hazard Ratio IV, Fixed, 95% CI
40.1.1 Mortality post-TAVI - 1 year - adjusted					
Fischer-Rasokat, 2020	0.2776	0.2743	428	222	1.32 [0.77, 2.26]

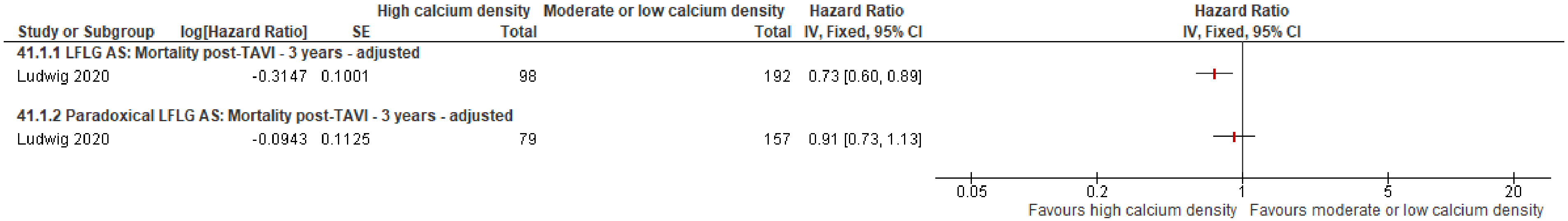
Figure 29: Aortic valve leaflet calcification >382 mm^3 compared to ≤382 mm^3 on CT in symptomatic severe AS



Study or Subgroup	log[Hazard Ratio]	SE	Hazard Ratio IV, Fixed, 95% CI
42.1.1 All-cause mortality post-TAVI - 2 years - adjusted			
Yoon 2020 (1)	0.8459	0.2563	2.33 [1.41, 3.85]
42.1.2 Cardiovascular mortality post-TAVI - 2 years - adjusted			
Yoon 2020	1.0403	0.3664	2.83 [1.38, 5.80]

Footnotes
(1) Numbers in each group not stated

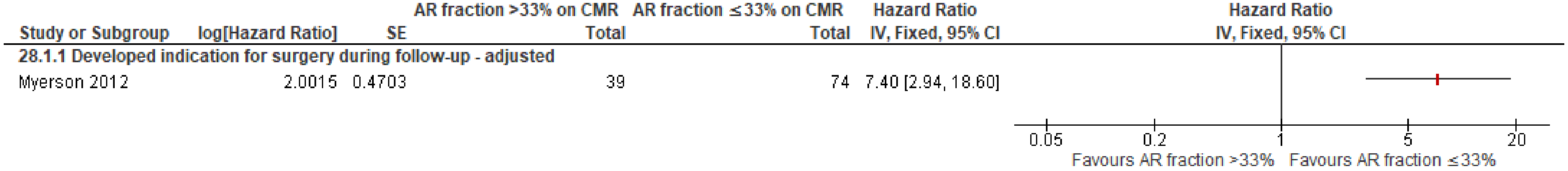
Figure 30: Aortic valve calcium density tertiles on CT (highest vs other tertiles) in severe AS undergoing TAVI



Study or Subgroup	log[Hazard Ratio]	SE	High calcium density Total	Moderate or low calcium density Total	Hazard Ratio IV, Fixed, 95% CI
41.1.1 LFLG AS: Mortality post-TAVI - 3 years - adjusted					
Ludwig 2020	-0.3147	0.1001	98	192	0.73 [0.60, 0.89]
41.1.2 Paradoxical LFLG AS: Mortality post-TAVI - 3 years - adjusted					
Ludwig 2020	-0.0943	0.1125	79	157	0.91 [0.73, 1.13]

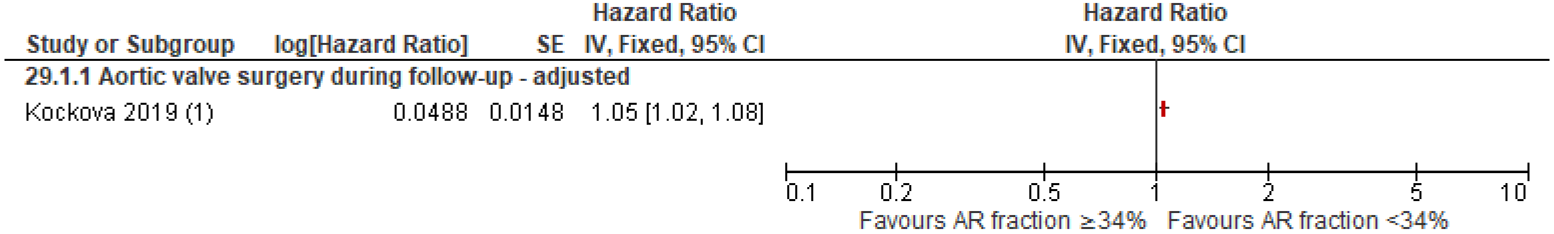
E.6 Aortic regurgitation

Figure 31: AR fraction >33% vs ≤33% vs. on cardiac MRI in asymptomatic moderate or severe chronic AR



Study or Subgroup	log[Hazard Ratio]	SE	AR fraction >33% on CMR Total	AR fraction ≤33% on CMR Total	Hazard Ratio IV, Fixed, 95% CI
28.1.1 Developed indication for surgery during follow-up - adjusted					
Myerson 2012	2.0015	0.4703	39	74	7.40 [2.94, 18.60]

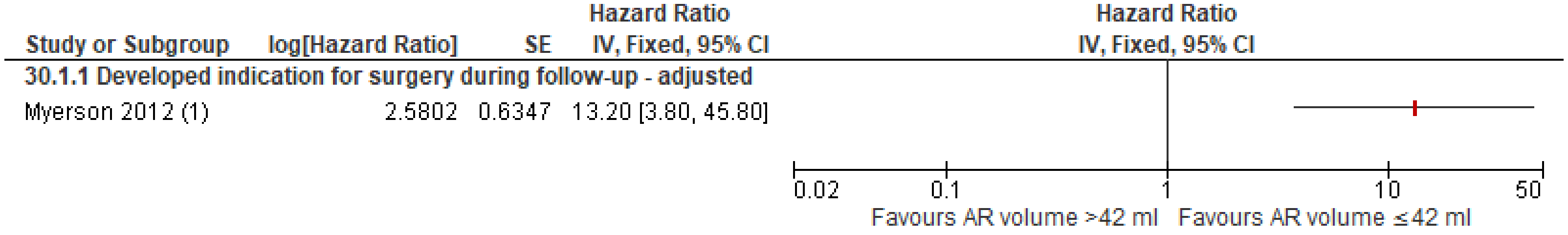
Figure 32: AR fraction ≥34% vs <34% on cardiac MRI in asymptomatic moderate-severe or severe AR



Study or Subgroup	log[Hazard Ratio]	SE	Hazard Ratio IV, Fixed, 95% CI
29.1.1 Aortic valve surgery during follow-up - adjusted			
Kockova 2019 (1)	0.0488	0.0148	1.05 [1.02, 1.08]

Footnotes
(1) Number in each group not reported

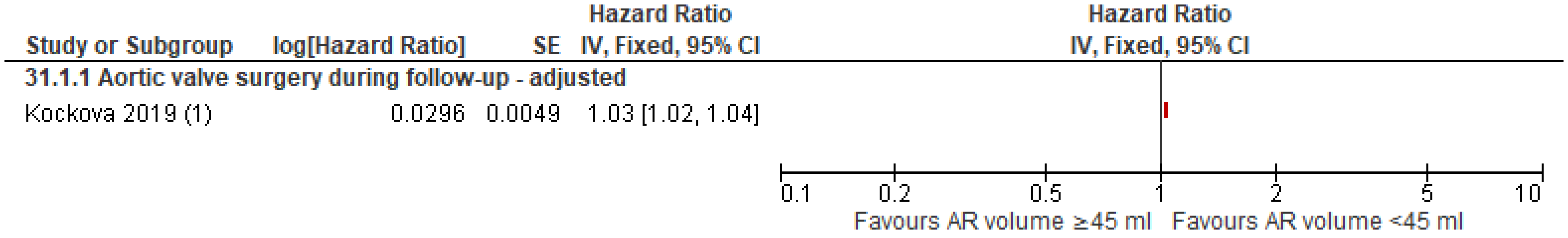
Figure 33: AR volume >42 ml vs ≤42 ml on cardiac MRI in asymptomatic moderate or severe chronic AR



Study or Subgroup	log[Hazard Ratio]	SE	Hazard Ratio IV, Fixed, 95% CI
30.1.1 Developed indication for surgery during follow-up - adjusted			
Myerson 2012 (1)	2.5802	0.6347	13.20 [3.80, 45.80]

Footnotes
(1) Number in each group not reported

Figure 34: AR volume ≥45 ml vs <45 ml on cardiac MRI in asymptomatic moderate-severe or severe AR

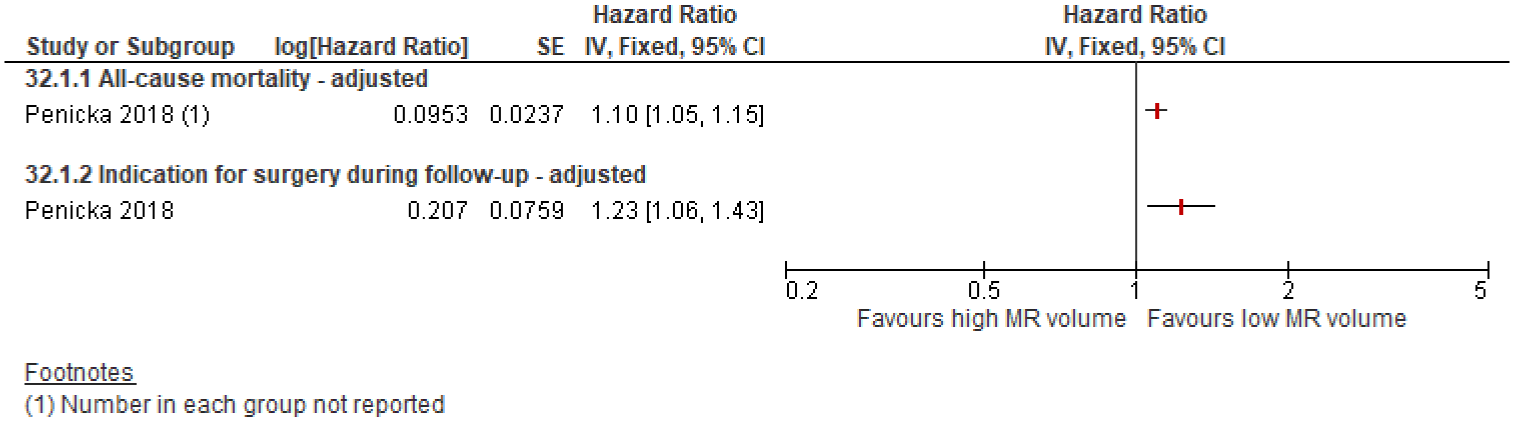


Study or Subgroup	log[Hazard Ratio]	SE	Hazard Ratio IV, Fixed, 95% CI
31.1.1 Aortic valve surgery during follow-up - adjusted			
Kockova 2019 (1)	0.0296	0.0049	1.03 [1.02, 1.04]

Footnotes
(1) Number in each group not reported

E.7 Mitral regurgitation

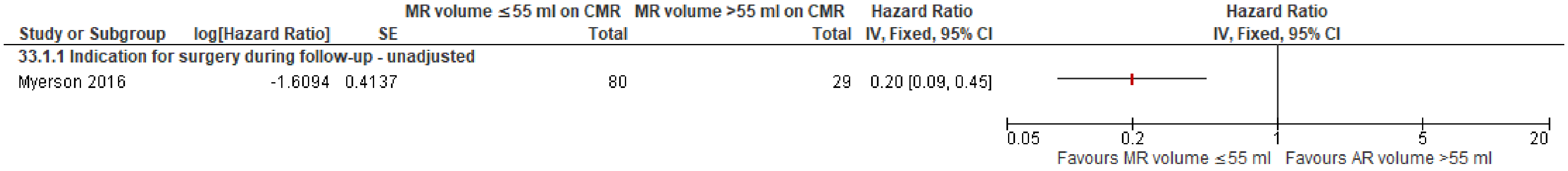
Figure 35: MR volume per 10 ml on cardiac MRI in in asymptomatic moderate or severe chronic organic MR



Study or Subgroup	log[Hazard Ratio]	SE	Hazard Ratio IV, Fixed, 95% CI
32.1.1 All-cause mortality - adjusted			
Penicka 2018 (1)	0.0953	0.0237	1.10 [1.05, 1.15]
32.1.2 Indication for surgery during follow-up - adjusted			
Penicka 2018	0.207	0.0759	1.23 [1.06, 1.43]

Footnotes
(1) Number in each group not reported

Figure 36: MR volume ≤55 ml compared with >55 ml on cardiac MRI in in asymptomatic moderate or severe chronic MR



Study or Subgroup	log[Hazard Ratio]	SE	MR volume ≤55 ml on CMR Total	MR volume >55 ml on CMR Total	Hazard Ratio IV, Fixed, 95% CI
33.1.1 Indication for surgery during follow-up - unadjusted					
Myerson 2016	-1.6094	0.4137	80	29	0.20 [0.09, 0.45]

E.8 Tricuspid regurgitation

Figure 37: RVEF per 5% higher (continuous variable) on cardiac MRI in severe isolated functional TR undergoing TR surgery (54.7% in NYHA class III/IV)

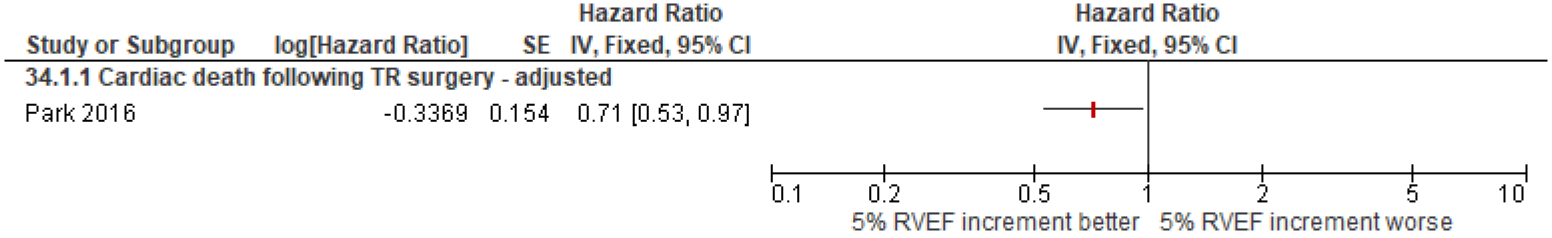


Figure 38: RVEF <46% vs ≥46% on cardiac MRI in severe isolated functional TR undergoing TR surgery (54.7% in NYHA class III/IV)

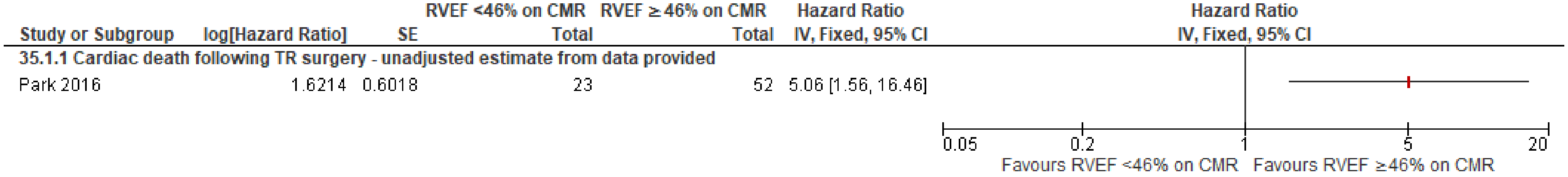


Figure 39: RV-ESVI 10 ml/m^2 increase (continuous variable) on cardiac MRI in severe isolated functional TR undergoing TR surgery (54.7% in NYHA class III/IV)

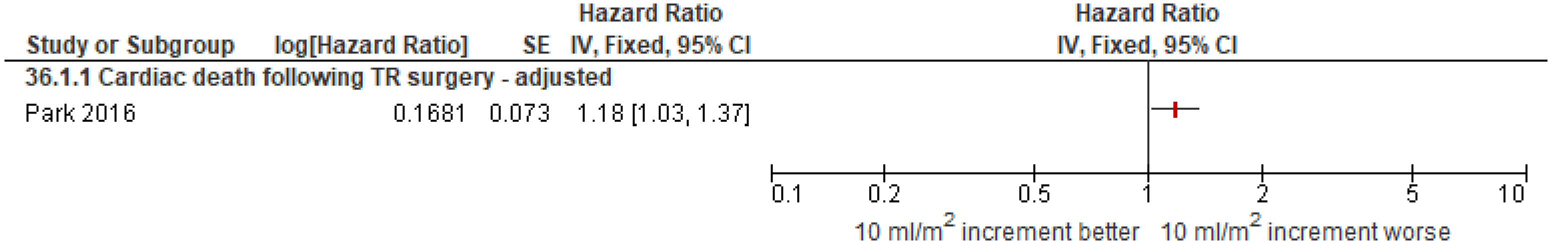


Figure 40: RV-ESVI ≥76 ml/m^2 vs. <76 ml/m^2 on cardiac MRI in severe isolated functional TR undergoing TR surgery (54.7% in NYHA class III/IV)

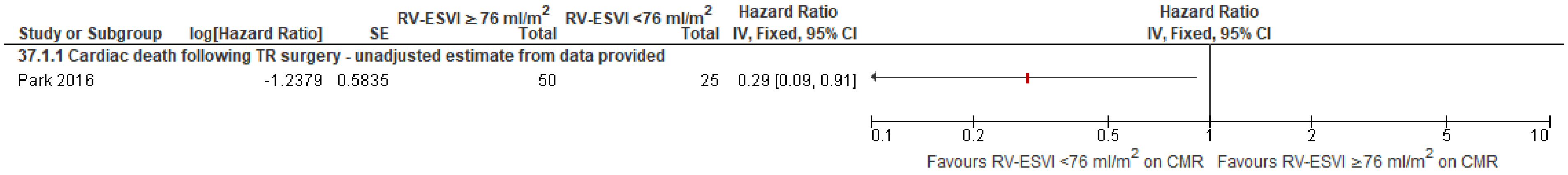


Figure 41: RVEF per 5% higher (continuous variable) on cardiac MRI in severe isolated functional TR undergoing TR surgery (54.7% in NYHA class III/IV)

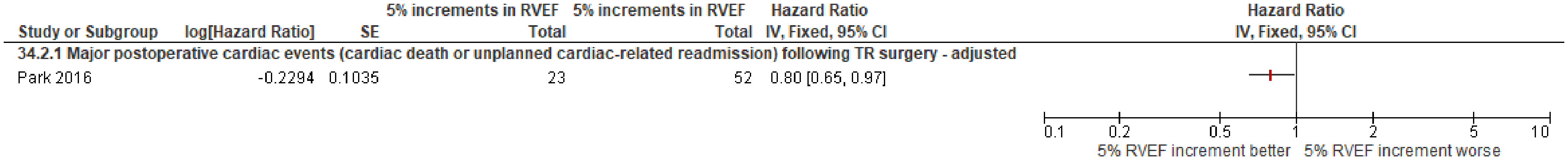
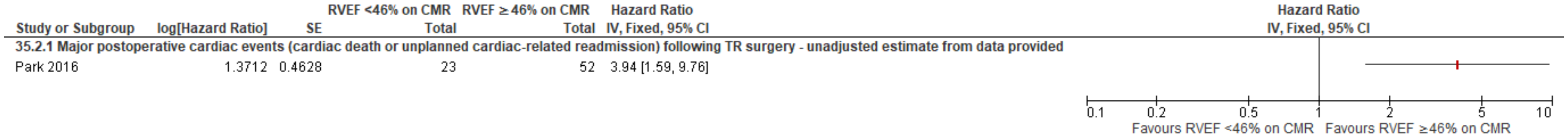
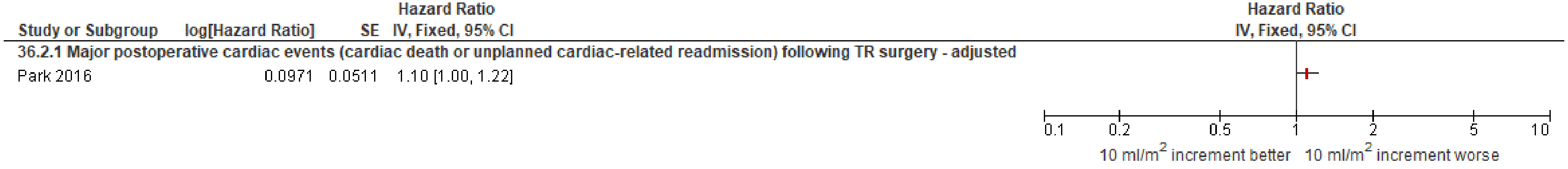


Figure 42: RVEF <46% vs ≥46% on cardiac MRI in severe isolated functional TR undergoing TR surgery (54.7% in NYHA class III/IV)



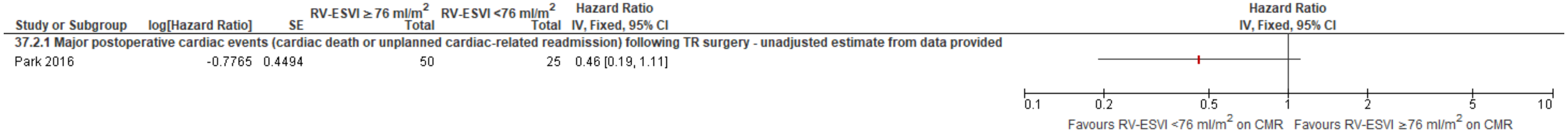
Study or Subgroup	log[Hazard Ratio]	SE	RVEF <46% on CMR Total	RVEF ≥ 46% on CMR Total	Hazard Ratio IV, Fixed, 95% CI
35.2.1 Major postoperative cardiac events (cardiac death or unplanned cardiac-related readmission) following TR surgery - unadjusted estimate from data provided					
Park 2016	1.3712	0.4628	23	52	3.94 [1.59, 9.76]

Figure 43: RV-ESVI 10 ml/m² increase (continuous variable) on cardiac MRI in severe isolated functional TR undergoing TR surgery (54.7% in NYHA class III/IV)



Study or Subgroup	log[Hazard Ratio]	SE	Hazard Ratio IV, Fixed, 95% CI
36.2.1 Major postoperative cardiac events (cardiac death or unplanned cardiac-related readmission) following TR surgery - adjusted			
Park 2016	0.0971	0.0511	1.10 [1.00, 1.22]

Figure 44: RV-ESVI ≥76 ml/m² vs. <76 ml/m² on cardiac MRI in severe isolated functional TR undergoing TR surgery (54.7% in NYHA class III/IV)



Study or Subgroup	log[Hazard Ratio]	SE	RV-ESVI ≥ 76 ml/m² Total	RV-ESVI <76 ml/m² Total	Hazard Ratio IV, Fixed, 95% CI
37.2.1 Major postoperative cardiac events (cardiac death or unplanned cardiac-related readmission) following TR surgery - unadjusted estimate from data provided					
Park 2016	-0.7765	0.4494	50	25	0.46 [0.19, 1.11]

Appendix F – GRADE tables

F.1 Aortic stenosis – left ventricular ejection fraction (LVEF) on cardiac MRI

Table 14: Clinical evidence profile: LVEF on cardiac MRI

Quality assessment							No of patients		Effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LVEF on cardiac MRI**	**Control**	**Relative (95% CI)**	
LVEF <50% compared to ≥50% for predicting all-cause mortality following aortic valve intervention - adjusted HR (Severe AS scheduled for aortic valve intervention) (follow-up median 3.8 years)										
1	cohort studies	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	71	369	HR 1.53 (0.76 to 3.06)	⊕○○○ VERY LOW
LVEF <50% compared to ≥50% for predicting adverse cardiac events after aortic valve intervention - unadjusted (Severe AS scheduled for aortic valve intervention) (follow-up median 38.8 months)										
1	cohort studies	very serious[1]	no serious inconsistency	serious[4]	serious[3]	none	43		HR 1.6 (0.57 to 4.5)	⊕○○○ VERY LOW
LVEF 30-49% compared to ≥50% for predicting all-cause mortality following TAVI - unadjusted (AS undergoing TAVI) (follow-up median 850 days)										
1	cohort studies	very serious[1]	no serious inconsistency	very serious[5]	serious[3]	none	65	108	HR 1.19 (0.69 to 2.04)	⊕○○○ VERY LOW
LVEF <30% vs ≥50% for predicting all-cause mortality following TAVI - unadjusted (AS undergoing TAVI) (follow-up median 850 days)										

1	cohort studies	very serious[1]	no serious inconsistency	very serious[5]	no serious imprecision	none	14	108	HR 2.54 (1.17 to 5.53)	⊕OOO VERY LOW

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Population - all already have an indication for intervention as scheduled for aortic valve intervention
[3] 95% CI crosses null line
[4] Population - all already scheduled for AVR so no uncertainty as to whether there is an indication for intervention prior to cardiac MRI; and outcome - composite of multiple outcomes in the protocol combined rather than reported separately
[5] Population - all already have an indication for intervention as scheduled for TAVI; and prognostic factor - splits LVEF into two separate thresholds compared with the same referent rather than using a single threshold. Also some uncertainty as to whether measured on CMR or echocardiography, though overall details suggest this is CMR measurements

F.2 Aortic stenosis – myocardial fibrosis on cardiac MRI

Table 15: Clinical evidence profile: myocardial fibrosis on cardiac MRI

Quality assessment							No of patients		Effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Myocardial fibrosis on cardiac MRI**	**Control**	**Relative (95% CI)**	
Midwall fibrosis LGE pattern vs no LGE for predicting all-cause mortality (mixed medical/surgical treatment) - adjusted HR (moderate or severe AS) (follow-up mean 2.0 years)										
1	cohort studies	very serious[1]	no serious inconsistency	very serious[2]	no serious imprecision	none	54	49	HR 5.35 (1.17 to 24.56)	⊕OOO VERY LOW
Infarct fibrosis LGE pattern vs no LGE for predicting all-cause mortality (mixed medical/surgical treatment) - adjusted HR (moderate or severe AS) (follow-up mean 2.0 years)										
1	cohort studies	very serious[1]	no serious inconsistency	very serious[2]	serious[3]	none	40	49	HR 2.56 (0.48 to 13.65)	⊕OOO VERY LOW

Mild fibrosis compared to no fibrosis for predicting all-cause mortality following AVR - Adjusted for age and sex (symptomatic severe AS undergoing AVR) (follow-up 10 years 9 months (57/58 patients enrolled - 46 analysed for fibrosis))										
1	cohort studies	very serious[1]	no serious inconsistency	very serious[4]	serious[3]	none	Not reported	Not reported	HR 2.52 (0.6 to 10.66)	⊕OOO VERY LOW
Mild fibrosis compared to no fibrosis for predicting all-cause mortality following AVR - Adjusted for EuroSCORE (symptomatic severe AS undergoing AVR) (follow-up 10 years 9 months (57/58 patients enrolled - 46 analysed for fibrosis))										
1	cohort studies	very serious[1]	no serious inconsistency	very serious[4]	serious[3]	none	Not reported	Not reported	HR 2.98 (0.74 to 11.96)	⊕OOO VERY LOW
Severe fibrosis vs no fibrosis for predicting all-cause mortality following AVR - Adjusted for age and sex (symptomatic severe AS undergoing AVR) (follow-up 10 years 9 months (57/58 patients enrolled - 46 analysed for fibrosis))										
1	cohort studies	very serious[1]	no serious inconsistency	very serious[4]	no serious imprecision	none	Not reported	Not reported	HR 6.03 (1.66 to 21.91)	⊕OOO VERY LOW
Severe fibrosis vs no fibrosis for predicting all-cause mortality following AVR - Adjusted for EuroSCORE (symptomatic severe AS undergoing AVR) (follow-up 10 years 9 months (57/58 enrolled - 46 analysed for fibrosis))										
1	cohort studies	very serious[1]	no serious inconsistency	very serious[4]	serious[3]	none	Not reported	Not reported	HR 3.7 (0.93 to 14.72)	⊕OOO VERY LOW
LGE vs no LGE for predicting all-cause mortality and unexpected hospitalisation for HF during follow-up (mixed medical and surgical treatment) - adjusted HR (moderate or severe AS) (follow-up median 27.9 months)										
1	cohort studies	very serious[1]	no serious inconsistency	very serious[5]	no serious imprecision	none	41	86	HR 1.56 (1.05 to 2.32)	⊕OOO VERY LOW
Fibrosis vs no fibrosis for predicting unplanned hospital admission (for AF, HF or ACS), aortic valve replacement or death - adjusted HR (asymptomatic severe AS) (follow-up median 358 days[6])										
1	cohort studies	very serious[1]	no serious inconsistency	serious[7]	serious[3]	none	21	57	HR 1.17 (0.44 to 3.11)	⊕OOO VERY LOW

LGE vs no LGE for predicting mortality, LVEF drop ≥2, new-onset HF or hospitalisation for cardiovascular causes and new-onset arrythmia (mixed medical/surgical treatment) - adjusted HR (severe AS) (follow-up mean 13 months)										
1	cohort studies	very serious[1]	no serious inconsistency	very serious[8]	serious[3]	none	46	63	OR 1.68 (0.60 to 4.6)	⊕OOO VERY LOW
LGE vs no LGE for predicting major adverse cardiac events - sudden cardia death, non-fatal myocardial infarction, sustained ventricular arrhythmias, third-degree AV block and hospitalisation for HF - adjusted HR (severe AS having AVR) (follow-up median 386 days)										
1	cohort studies	serious[1]	no serious inconsistency	very serious[9]	no serious imprecision	none	30	22	HR 11.3 (1.82 to 70.18)	⊕OOO VERY LOW
LGE vs no LGE for predicting all-cause mortality post-intervention - adjusted HR (severe AS having valve intervention) (follow-up median 2.9-3.8 years)										
3	cohort studies	very serious[1]	no serious inconsistency	serious[10]	no serious imprecision	none	605	602	HR 1.94 (1.34 to 2.8)	⊕OOO VERY LOW
LGE vs no LGE for predicting cardiovascular mortality post-intervention - adjusted HR (severe AS having valve intervention) (follow-up median 3.6 years)										
1	cohort studies	serious[1]	no serious inconsistency	serious[10]	no serious imprecision	none	341	272	HR 3.14 (1.65 to 5.98)	⊕⊕OO LOW
Diffuse myocardial fibrosis vs normal myocardium for predicting cardiovascular death, hospitalisation for cardiac causes, non-fatal stroke and symptomatic aggravation (worsening NYHA class) following AVR - adjusted HR (severe AS undergoing AVR) (follow-up median 38.8 months)										
1	cohort studies	very serious[1]	no serious inconsistency	very serious[11]	no serious imprecision	none	30	13	HR 5.52 (1.03 to 29.51)	⊕OOO VERY LOW

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Population - unclear whether indication for intervention was unclear in all patients, as includes some that underwent AVR which may have been scheduled prior to CMR; prognostic factor - provides results separately for two types of LGE on CMR rather than as a single combined result vs. no LGE on CMR; and outcome - includes those with and without surgery during follow-up, whereas ideally aimed to look at results for operative and non-operative mortality separately
[3] 95% CI crosses null line
[4] Population - all were symptomatic severe AS undergoing AVR, so already have an indication for intervention prior to CMR; and prognostic factor - specific severity of fibrosis on CMR compared with no fibrosis rather than comparing any fibrosis with no fibrosis

[5] Population - includes a large proportion that were already deemed to have an indication for intervention regardless of CMR results; and outcome - composite outcome of multiple outcomes in protocol combined rather than reported separately. Also includes those with and without operation in the analysis, whereas ideally aimed to analyse operative and non-operative outcomes separately.
[6] This was for the whole cohort of 92 patients and not limited to the 72 included in fibrosis analysis
[7] Outcome - composite of three separate outcomes listed in the protocol rather than reporting them separately
[8] Population - 35% already deemed to have indications for intervention regardless of CMR results; and outcome - composite of multiple factors listed in protocol, as well as some not listed in protocol, rather than reporting separately. Also includes medically managed and surgically managed patients in the same analysis, whereas ideally aimed to analyse postoperative and non-operative outcomes separately.
[9] Population - indication for intervention already present as population was severe AS patients undergoing AVR; and outcome - composite of multiple outcomes including some of those in protocol as well as additional ones
[10] Population - all already scheduled for AVR so does not represent population where there is uncertainty about whether or not intervention is indicated
[11] Population - all already scheduled for AVR so no uncertainty as to whether there is an indication for intervention prior to CMR; and outcome - composite of multiple outcomes in the protocol combined rather than reported separately

F.3 Aortic stenosis – coronary artery disease on cardiac CT

Table 16: Clinical evidence profile: coronary artery disease on cardiac CT

Quality assessment							No of patients		Effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Coronary artery disease on cardiac CT**	**Control**	**Relative (95% CI)**	
Significant stenosis (>5 luminal diameter) of 1, 2 or 3 vessels or atheromatosis compared to normal coronary angiogram for predicting indication for AVR - unadjusted (Asymptomatic moderate-severe AS with no indication for AVR) (follow-up median 2.3 years)										
1	cohort studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	36/85 (42.4%)	7/19 (36.8%)	RR 1.15 (0.61 to 2.18)	⊕OOO VERY LOW

Significant stenosis (>50% luminal diameter) of 1, 2 or 3 vessels vs normal coronary angiogram or atheromatosis for predicting indication for AVR - unadjusted RR (Asymptomatic moderate-severe AS with no indication for AVR) (follow-up median 2.3 years)										
1	cohort studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	16/32 (50%)	27/72 (37.5%)	RR 1.33 (0.84 to 2.11)	⊕OOO VERY LOW
CAD >70% stenosis compared to ≤70% stenosis for predicting indication for AVR - unadjusted (asymptomatic mild-severe AS) (follow-up median 27 months)										
1	cohort studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	19	97	HR 1.79 (0.93 to 3.44)	⊕OOO VERY LOW
Multivessel obstructive CAD compared to no multivessel obstructive CAD for predicting cardiac events - cardiac death, AVR, non-fatal myocardial infarction and HF requiring urgent hospitalisation - adjusted HR (asymptomatic mild-severe AS) (follow-up median 29 months)										
1	cohort studies	very serious[1]	no serious inconsistency	very serious[3]	serious[2]	none	11	53	HR 2.7 (0.95 to 7.65)	⊕OOO 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] 95% CI crosses null line
[3] Population - unclear whether there is uncertainty regarding indication for intervention in all patents, as includes mild-severe asymptomatic AS patients, with only 45% being asymptomatic severe; and outcome - composite of multiple outcomes specified in the protocol rather than being reported separately

F.4 Aortic stenosis – aortic valve area on cardiac CT

Table 17: Clinical evidence profile: aortic valve area on cardiac CT

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aortic valve area on CT	Control	Relative (95% CI)		
Aortic valve area ≤1.2 cm2 vs >1.2 cm2 for predicting mortality under medical treatment - adjusted for age-adjusted Charlson score index, sex, symptoms, mean gradient and LVEF (symptomatic/asymptomatic AS) (follow-up mean 3.2 years)											
1	cohort studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	175	94	HR 3.16 (1.6 to 6.26)	⊕⊕⊕O MODERATE	
Aortic valve area ≤1.0 cm2 vs >1.0 cm2 for predicting mortality under medical treatment - adjusted for age-adjusted Charlson score index, sex, symptoms, mean gradient and LVEF (symptomatic/asymptomatic AS) (follow-up mean 3.2 years)											
1	cohort studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	126	143	HR 1.43 (0.77 to 2.64)	⊕⊕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 null line

F.5 Aortic stenosis – aortic valve calcium score on cardiac CT

Table 18: Clinical evidence profile: Aortic valve calcification on cardiac CT

Quality assessment							No of patients		Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Calcium score high	Calcium score normal	Relative (95% CI)	
Severe aortic valve calcification (≥2065 AU in men and ≥1274 in women) compared to non-severe aortic valve calcification (<2065 AU in men and <1274 AU in women) for predicting mortality under conservative treatment - adjusted HR (at least mild AS under conservative management) (follow-up mean 1.7 years)										
1	cohort studies	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	410	384	HR 1.75 (1.04 to 2.93)	⊕OOO VERY LOW

Severe aortic valve calcification (≥2065 AU in men and ≥1274 in women) compared to non-severe aortic valve calcification (<2065 AU in men and <1274 AU in women) for predicting death or AVR during follow-up - adjusted HR (AS of various severities and symptom status) (follow-up median 1029 days)										
1	cohort studies	very serious[1]	no serious inconsistency	serious[3]	no serious imprecision	none	Not reported	Not reported	HR 3.8 (2.16 to 6.69)	⊕○○○ VERY LOW
≥723 compared to <723 AU for predicting cardiac events - cardiac death, AVR, non-fatal myocardial infarction and HF requiring urgent hospitalisation - unadjusted (asymptomatic, mild to severe AS) (follow-up median 29 months)										
1	cohort studies	very serious[1]	no serious inconsistency	very serious[4]	no serious imprecision	none	32	32	HR 6.08 (2.86 to 12.92)	⊕○○○ VERY LOW
≥723 compared to <723 for predicting non-AVR cardiac events - cardiac death, non-fatal myocardial infarction and HF requiring urgent hospitalisation - unadjusted (asymptomatic, mild to severe AS) (follow-up median 29 months)										
1	cohort studies	very serious[1]	no serious inconsistency	very serious[4]	no serious imprecision	none	32	32	HR 3.69 (1.39 to 9.82)	⊕○○○ VERY LOW
≥1266 vs <1266 for predicting cardiac events - cardiac death, AVR, non-fatal myocardial infarction and HF requiring urgent hospitalisation - unadjusted (asymptomatic severe AS)										
1	cohort studies	very serious[1]	no serious inconsistency	very serious[5]	serious[6]	none	14	15	HR 1.71 (0.71 to 4.13)	⊕○○○ VERY LOW
≥1266 vs <1266 for predicting non-AVR cardiac events - cardiac death, non-fatal myocardial infarction and HF requiring urgent hospitalisation - unadjusted (asymptomatic severe AS)										
1	cohort studies	very serious[1]	no serious inconsistency	very serious[5]	serious[6]	none	14	15	HR 3.08 (0.85 to 11.19)	⊕○○○ VERY LOW
>6,000 HU vs ≤6,000 HU for predicting rehospitalisation - adjusted HRs (undergoing TAVI) (follow-up 1 month post-TAVI) (follow-up 1 months)										
1	cohort studies	very serious[1]	no serious inconsistency	very serious[7]	no serious imprecision	none	118		OR 23.24 (3.59 to 150.38)	⊕○○○ VERY LOW

>6,000 HU vs ≤6,000 HU for predicting all-cause mortality, stroke, myocardial infarction, heart failure or rehospitalisation for cardiac causes - adjusted HRs (undergoing TAVI) (follow-up 1 month post-TAVI)										
1	cohort studies	very serious[1]	no serious inconsistency	very serious[8]	no serious imprecision	none	118		OR 106 (15.44 to 727.53)	⊕OOO VERY LOW
>2027 compared to ≤2027 AU for predicting mortality post-AVR - 30 days - unadjusted (low-flow, low-gradient severe AS)										
1	cohort studies	very serious[1]	no serious inconsistency	serious[9]	serious[6]	none	10	11	HR 1 (0.1 to 10)	⊕OOO VERY LOW
Calcium score ≥1200 vs <1200 in women and ≥2000 vs <2000 AU in men for predicting mortality post-TAVI - 1 year – adjusted (severe AS scheduled for TAVI)										
1	randomised trials	very serious[1]	no serious inconsistency	serious[10]	serious[6]	none	428	222	HR 1.32 (0.77 to 2.26)	⊕OOO VERY LOW
Leaflet calcification >382 vs <382 mm3 for predicting all-cause mortality post-TAVI - 2 years – adjusted (severe AS with bicuspid valve scheduled for TAVI)										
1	randomised trials	serious[1]	no serious inconsistency	serious[11]	no serious imprecision	none	1034		HR 2.33 (1.41 to 3.85)	⊕⊕OO LOW
Calcium density highest tertile vs moderate or low tertile for predicting mortality post-TAVI - 3 years – adjusted (severe low-flow, low-gradient AS)										
1	randomised trials	serious[1]	no serious inconsistency	serious[11]	no serious imprecision	none	98	192	HR 0.73 (0.6 to 0.89)	⊕⊕OO LOW
Calcium density highest tertile vs moderate or low tertile in paradoxical LFLG AS for predicting mortality post-TAVI - 3 years – adjusted (severe paradoxical low-flow, low-gradient AS)										
1	randomised trials	serious[1]	no serious inconsistency	serious[11]	serious[6]	none	79	157	HR 0.91 (0.73 to 1.13)	⊕OOO VERY LOW
Leaflet calcification >382 vs <382 mm3 for predicting cardiovascular mortality post-TAVI - 2 years – adjusted (severe AS with bicuspid valve scheduled for TAVI)										

1	randomised trials	very serious[1]	no serious inconsistency	serious[11]	no serious imprecision	none	1034	HR 2.83 (1.38 to 5.8)	⊕OOO VERY LOW

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

[2] Population - unclear whether this represents a population where there was uncertainty about whether or not to intervene as includes mild-severe AS under conservative management

[3] Outcome - composite outcome of two separate outcomes listed in the protocol, rather than reporting separately. Also unclear whether AVR captures only unplanned intervention as in our protocol, or whether some were planned procedures following CT results.

[4] Population - unclear whether represents a population where there is uncertainty about whether or not to intervene, as includes mixture of mild-severe asymptomatic AS with only 45% severe; prognostic factor - threshold is quite different to that specified in the protocol and the same one has been used for men and women, rather than using a separate threshold; and outcome - composite outcome consisting of multiple outcomes listed in the protocol rather than reporting separately.

[5] Prognostic factor - threshold is quite different to that specified in the protocol and the same one has been used for men and women, rather than using a separate threshold; and outcome - composite outcome consisting of multiple outcomes listed in the protocol rather than reporting separately.

[6] 95% CI crosses null line

[7] Population - all had TAVI so already an indication for intervention; and prognostic factor - threshold of 6,000 HU used very different to suggested thresholds in protocol and same one used for men and women.

[8] Population - all had TAVI so already an indication for intervention; prognostic factor - threshold of 6,000 HU used very different to suggested thresholds in protocol and same one used for men and women; and outcome - composite outcome of multiple outcomes in protocol as well as some additional outcomes not listed in protocol

[9] Prognostic factor - same threshold used for men and women rather than a separate one as in protocol

[10] Population - all had TAVI so already an indication for intervention

[11] Population - all had TAVI so already an indication for intervention; and prognostic factor - calcium density, not calcium score threshold as stated in the protocol

F.6 Aortic regurgitation – regurgitant fraction or volume on cardiac MRI

Table 19: Clinical evidence profile: AR fraction or volume on cardiac MRI

Quality assessment							No of patients		Effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Regurgitant fraction or volume on cardiac MRI**	**Control**	**Relative (95% CI)**	
AR fraction ≤33% vs >33% for predicting indication for surgery during follow-up - adjusted HR (Asymptomatic moderate/severe AR) (follow-up mean 2.6 years)										

1	cohort studies	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	74	39	HR 7.4 (2.94 to 18.6)	⊕⊕OO LOW
AR fraction <34% vs ≥34% for predicting aortic valve surgery during follow-up - adjusted for MRI-derived LV volumes or their indices (Asymptomatic severe AR) (follow-up median 587 days)										
1	cohort studies	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	104		HR 1.05 (1.02 to 1.08)	⊕⊕OO LOW
AR volume ≤42 ml vs >42 ml for predicting indication for surgery during follow-up - adjusted HR (Asymptomatic moderate/severe AR) (follow-up mean 2.6 years)										
1	cohort studies	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	74	39	HR 13.2 (3.8 to 45.8)	⊕⊕OO LOW
AR volume <45 ml vs ≥45 ml for predicting aortic valve surgery during follow-up - adjusted HR (Asymptomatic severe AR) (follow-up median 587 days)										
1	cohort studies	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	104		HR 1.03 (1.02 to 1.04)	⊕⊕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

F.7 Mitral regurgitation – regurgitant volume on cardiac MRI

Table 20: Clinical evidence profile: MR volume on cardiac MRI

Quality assessment							**No of patients**		**Effect**	**Quality**
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Mitral valve regurgitant volume on cardiac MRI**	**Control**	**Relative (95% CI)**	
MR volume per 10 ml for predicting all-cause mortality - adjusted (asymptomatic moderate or severe MR) (follow-up median 5 years)										

1	cohort studies	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	258		HR 1.10 (1.05 to 1.15)	⊕⊕OO LOW
MR volume per 10 ml for predicting indication for surgery - adjusted (asymptomatic moderate or severe MR) (follow-up median 5 years)										
1	cohort studies	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	258		HR 1.23 (1.06 to 1.43)	⊕⊕OO LOW
MR volume ≤55 ml vs >55 ml for predicting indication for surgery during follow-up - unadjusted (asymptomatic moderate or severe MR) (follow-up mean 2.5 years)										
1	cohort studies	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	80	29	HR 0.2 (0.09 to 0.45)	⊕⊕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

F.8 Tricuspid regurgitation – right ventricular function on cardiac MRI

Table 21: Clinical evidence profile: Right ventricular function on cardiac MRI

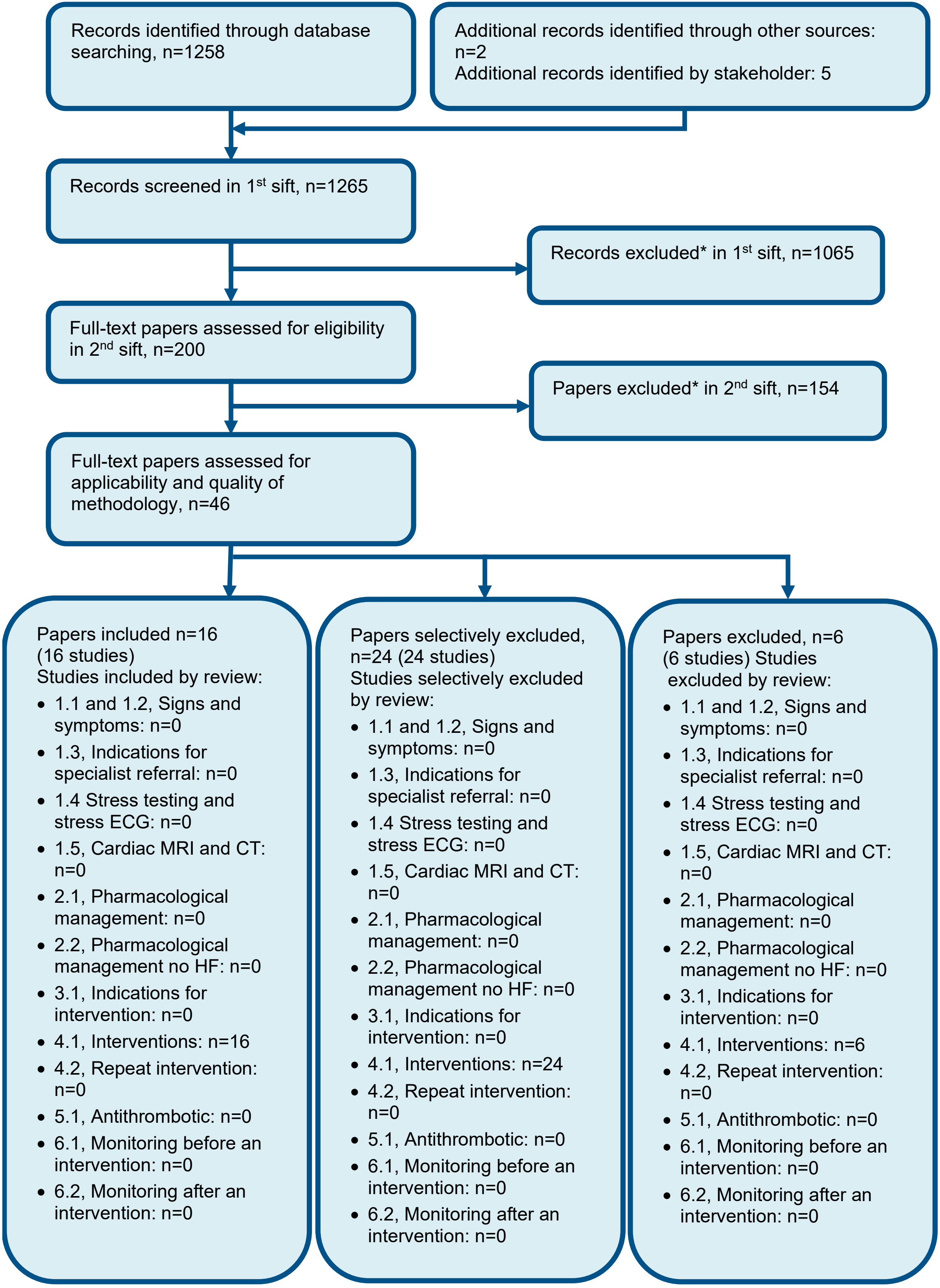
Quality assessment							No of patients		Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Right ventricular function on CMR	Control	Relative (95% CI)	
RVEF per 5% higher to predict cardiac death following TR surgery - adjusted HR (Severe isolated functional TR and underwent isolated TR surgery) (follow-up median 57 months)										
1	cohort studies	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	75		HR 0.71 (0.53 to 0.97)	⊕OOO VERY LOW

RVEF <46% vs ≥46% to predict cardiac death following TR surgery - unadjusted estimate from data provided - Cardiac death following TR surgery - unadjusted estimate (Severe isolated functional TR and underwent isolated TR surgery) (follow-up median 57 months)										
1	cohort studies	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	23	52	HR 5.06 (1.56 to 16.46)	⊕OOO VERY LOW
10ml/m2 increments of RV-ESVI to predict cardiac death following TR surgery - adjusted HR (Severe isolated functional TR and underwent isolated TR surgery) (follow-up median 57 months)										
1	cohort studies	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	75		HR 1.18 (1.03 to 1.37)	⊕OOO VERY LOW
RV-ESVI ≥76 ml/m2 vs RV-ESVI <76 ml/m2 to predict cardiac death following TR surgery - unadjusted estimate (Severe isolated functional TR and underwent isolated TR surgery) (follow-up median 57 months)										
1	cohort studies	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	50	25	HR 0.29 (0.09 to 0.91)	⊕OOO VERY LOW
RVEF per 5% higher to predict major postoperative cardiac events (cardiac death or unplanned cardiac-related readmission) following TR surgery - adjusted HR (Severe isolated functional TR and underwent isolated TR surgery) (follow-up median 57 months)										
1	cohort studies	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	75		HR 0.8 (0.65 to 0.97)	⊕OOO VERY LOW
RVEF <46% vs ≥46% to predict major postoperative cardiac events (cardiac death or unplanned cardiac-related readmission) following TR surgery - unadjusted estimate from data provided - Major postoperative cardiac events (cardiac death or unplanned cardiac-related readmission) following TR surgery - unadjusted estimate (Severe isolated functional TR and underwent isolated TR surgery) (follow-up median 57 months)										
1	cohort studies	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	23	52	HR 3.94 (1.59 to 9.76)	⊕OOO VERY LOW
10ml/m2 increments of RV-ESVI to predict major postoperative cardiac events (cardiac death or unplanned cardiac-related readmission) following TR surgery - adjusted for age, sex, NYHA class, haemoglobin level and glomerular filtration rate - Major postoperative cardiac events (cardiac death or unplanned cardiac-related readmission) following TR surgery - adjusted HR (Severe isolated functional TR and underwent isolated TR surgery) (follow-up median 57 months)										
1	cohort studies	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	75		HR 1.1 (1 to 1.22)	⊕OOO VERY LOW
RV-ESVI ≥76 ml/m2 vs RV-ESVI <76 ml/m2 to predict major postoperative cardiac events (cardiac death or unplanned cardiac-related readmission) following TR surgery - unadjusted estimate (Severe isolated functional TR and underwent isolated TR surgery) (follow-up median 57 months)										

1	cohort studies	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	50	25	HR 0.46 (0.19 to 1.11)	⊕OOO VERY LOW

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Population - all underwent intervention for severe functional TR so does not represent population where there is uncertainty about whether there is an indication for intervention; and outcome - only includes cardiac deaths and not all deaths.
[3] 95% CI crosses null line

Appendix G – Health economic study selection



Records identified through database searching, n=1258

Additional records identified through other sources: n=2
Additional records identified by stakeholder: 5

Records screened in 1st sift, n=1265

Records excluded* in 1st sift, n=1065

Full-text papers assessed for eligibility in 2nd sift, n=200

Papers excluded* in 2nd sift, n=154

Full-text papers assessed for applicability and quality of methodology, n=46

Papers included n=16 (16 studies)
Studies included by review:

- 1.1 and 1.2, Signs and symptoms: n=0
- 1.3, Indications for specialist referral: n=0
- 1.4 Stress testing and stress ECG: n=0
- 1.5, Cardiac MRI and CT: n=0
- 2.1, Pharmacological management: n=0
- 2.2, Pharmacological management no HF: n=0
- 3.1, Indications for intervention: n=0
- 4.1, Interventions: n=16
- 4.2, Repeat intervention: n=0
- 5.1, Antithrombotic: n=0
- 6.1, Monitoring before an intervention: n=0
- 6.2, Monitoring after an intervention: n=0

Papers selectively excluded, n=24 (24 studies)
Studies selectively excluded by review:

- 1.1 and 1.2, Signs and symptoms: n=0
- 1.3, Indications for specialist referral: n=0
- 1.4 Stress testing and stress ECG: n=0
- 1.5, Cardiac MRI and CT: n=0
- 2.1, Pharmacological management: n=0
- 2.2, Pharmacological management no HF: n=0
- 3.1, Indications for intervention: n=0
- 4.1, Interventions: n=24
- 4.2, Repeat intervention: n=0
- 5.1, Antithrombotic: n=0
- 6.1, Monitoring before an intervention: n=0
- 6.2, Monitoring after an intervention: n=0

Papers excluded, n=6 (6 studies) Studies excluded by review:

- 1.1 and 1.2, Signs and symptoms: n=0
- 1.3, Indications for specialist referral: n=0
- 1.4 Stress testing and stress ECG: n=0
- 1.5, Cardiac MRI and CT: n=0
- 2.1, Pharmacological management: n=0
- 2.2, Pharmacological management no HF: n=0
- 3.1, Indications for intervention: n=0
- 4.1, Interventions: n=6
- 4.2, Repeat intervention: n=0
- 5.1, Antithrombotic: n=0
- 6.1, Monitoring before an intervention: n=0
- 6.2, Monitoring after an intervention: n=0

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

Appendix H – Economic evidence tables

None

Appendix I – Health economic model

None.

Appendix J – Excluded studies

Clinical studies

Table 22: Studies excluded from the clinical review

Reference	Reason for exclusion
Abdelaziz 2020[1]	Incorrect study design
Abdelghani 2020[2]	Insufficient analysis and incorrect prognostic factor
Abramowitz 2017[3]	Incorrect population
Abramowitz 2017[4]	Incorrect prognostic factors
Agasthi 2020[5]	Insufficient reporting of prognostic factor definitions
Akin 2010[7]	Incorrect study design - narrative review
Ali 2015[11]	Incorrect outcome and prognostic factors
Ancona 2017[12]	Incorrect prognostic factors
Anger 2014[13]	Incorrect outcome
Annabi 2018[14]	Incorrect study design - narrative review
Anyanwu 2006[15]	Incorrect study design - narrative review
Aquaro 2017[16]	Incorrect study design
Azevedo 2010[17]	Incorrect prognostic factors
Azzalini 2014[18]	Incorrect outcome prognostic factors
Balciunaite 2020[19]	Protocol only
Balciunaite 2020[20]	Incorrect study design - SR that did not identify many studies identified by this review
Barkagan 2017[21]	Incorrect outcome and prognostic factors
Becle 2020[23]	Incorrect prognostic factor: CAD not by CT and thoracic aortic not valve calcium
Bekeredjian 2015[24]	Incorrect outcome
Berger 2014[25]	Incorrect study design - narrative review
Bettinger 2017[26]	Incorrect outcome and prognostic factor
Bing 2019[27]	Incorrect study design - protocol only and no results published yet
Bing 2020[28]	Incorrect comparison - infarct LGE vs no or non-infarct
Borger 2004[29]	Incorrect prognostic factor
Bosmans 2016[30]	Incorrect outcome
Broyd 2018[31]	Incorrect population
Buckert 2018[32]	Incorrect prognostic factor and analysis
Buellesfeld 2014[33]	Incorrect outcome
Butter 2019[34]	Incorrect outcome
Calin 2020[35]	Incorrect study design - narrative review
Capoulade 2015[36]	Incorrect study design - narrative review

Reference	Reason for exclusion
Carmona 2020[37]	Incorrect prognostic factors - none matching protocol
Carrabba 2008[38]	Incorrect population and prognostic factors
Carrero 2019[39]	Incorrect prognostic factors - none matching protocol
Cavalcante 2017[41]	Incorrect prognostic factor
Cavalcante 2018[42]	Incorrect study design - narrative review
Chaikriangkrai 2014[43]	Incorrect prognostic factor
Chambers 2017[44]	Incorrect study design - narrative review
Chan 2011[45]	Incorrect prognostic factors
Chen 2018[46]	More recent SR available and insufficient reporting of included study characteristics. References checked.
Chew 2018[47]	Incorrect study design - narrative review
Chew 2019[48]	Incorrect prognostic factor
Chiang 1998[49]	Incorrect outcome
Chieffo 2016[51]	Incorrect prognostic factors
Chieffo 2018[50]	Incorrect prognostic factors
Chin 2016[52]	Incorrect prognostic factor
Chin 2017[53]	Incorrect analysis - unadjusted results only and sufficient studies with multivariate results for this prognostic factor
Cho 2017[54]	Incorrect prognostic factor
Choi 2020[55]	Incorrect prognostic factors - none matching protocol
Chourdakis 2018[56]	Incorrect study design - narrative review
Ciobotaru 2016[58]	Incorrect outcome
Cioffi 2011[59]	Incorrect prognostic factors
Citro 2018[60]	Incorrect study design - protocol only and no results published.
Clavel 2015[61]	Incorrect prognostic factors
Connelly 2017[64]	Incorrect study design - narrative review
Cortes 2016[65]	Incorrect prognostic factors and outcome
Czepluch 2016[66]	Incorrect prognostic factor and outcomes
Dahya 2016[69]	Incorrect prognostic factor and outcomes
Damluji 2020[70]	Incorrect prognostic factors - none matching protocol
D'Ancona 2017[67]	Incorrect comparison
D'Arcy 2011[68]	Abstract only
Delgado 2018[71]	Incorrect study design - narrative review
Della Corte 2019[72]	Incorrect study design - narrative review
Dencker 2016[73]	Incorrect prognostic factor and outcome
Di Martino 2015[74]	Incorrect outcome
Di Pasquale 2017[75]	Incorrect study design - narrative review
Diab 2008[76]	Incorrect study design - narrative review
Dichtl 2008[77]	Incorrect prognostic factor
Dinh 2010[78]	Incorrect prognostic factor
Dobson 2016[79]	Incorrect outcome
Duncan 2012[80]	Incorrect study design - narrative review
Dvir 2013[81]	Incorrect study design - narrative review
Dvir 2017[82]	Incorrect population and study design

Reference	Reason for exclusion
Dweck 2013[83]	Incorrect study design - narrative review
Eberhard 2017[85]	Incorrect prognostic factor
Emerson 2015[86]	Incorrect prognostic factor
Escarcega 2016[87]	Incorrect prognostic factor
Ewe 2011[89]	Incorrect outcome
Ferreira-Neto 2019[90]	Incorrect prognostic factor
Feuchtner 2006[92]	Incorrect outcome
Feuchtner 2013[91]	Incorrect outcome
Feyz 2018[93]	Incorrect population and prognostic factor
Flett 2012[95]	Incorrect outcome
Fonseca 2016[96]	Incorrect outcomes
Fraccaro 2011[97]	Incorrect outcome
Fujimiya 2019[98]	Incorrect outcomes
Fukui 2020[99]	Incorrect prognostic factors
Fusini 2015[100]	Incorrect study design and prognostic factors
Galvao Braga 2014[101]	Not in English language
Gegenava 2020[102]	Incorrect prognostic factors - none matching protocol
Gelfand 2007[104]	Incorrect study design - narrative review
Gelfand 2010[103]	Insufficient reporting of prognostic analysis
Girdauskas 2017[105]	Incorrect outcome
Goenka 2014[106]	Incorrect study design - narrative review
Guerrero 2016[107]	Incorrect study design:
Haensig 2012[109]	Incorrect prognostic factor
Haensig 2016[108]	Incorrect outcome
Hallett 2016[110]	Incorrect study design - narrative review
Hamdan 2015[111]	Incorrect prognostic factors and outcomes
Hansson 2016[112]	Incorrect prognostic factors and outcomes
Hansson 2017[113]	Incorrect prognostic factors and study design
Harbaoui 2016[114]	Incorrect prognostic factor
Harris 2017[115]	Incorrect population
Hayashida 2012[116]	Incorrect study design and prognostic factors
Hein-Rothweiler 2017[117]	Incorrect outcome
Herrmann 2011[119]	Incorrect study design and prognostic factors
Hiendlmayr 2016[120]	Incorrect study design - narrative review
Holy 2020[121]	Incorrect prognostic factors - none matching protocol
Huther 2011[122]	Incorrect population
Hwang 2017[124]	Incorrect prognostic factors and outcome
Hwang 2020[125]	Incorrect prognostic factors - none matching protocol
Jabbour 2011[126]	Incorrect prognostic factor and outcomes
Jilaihawi 2014[128]	Incorrect outcome
Jilaihawi 2016[127]	Incorrect prognostic factors

Reference	Reason for exclusion
Kaleschke 2011[129]	Incorrect study design - narrative review
Kammerlander 2019[130]	Incorrect population
Kaneko 2017[131]	Incorrect outcome
Khalique 2014[132]	Incorrect outcome
Kim 2018[133]	Incorrect prognostic factor
Kim 2018[135]	Incorrect study design - narrative review
Kim 2020[134]	Incorrect prognostic factors - none matching protocol
Kinnel 2020[136]	Incorrect prognostic factors - none matching protocol
Kitkungvan 2018[137]	Incorrect prognostic factors and outcomes
Ko 2020[138]	Incorrect prognostic factors and outcomes
Kochman 2016[139]	Incorrect prognostic factors and outcomes
Koh 2015[141]	Incorrect outcome
Kong 2016[142]	Incorrect outcome
Koos 2011[143]	Incorrect outcome
Koos 2013[144]	Insufficient data reported
Kumar 2010[145]	Incorrect study design - narrative review
Kusunose 2017[146]	Incorrect prognostic factors
Kwon 2016[147]	Incorrect prognostic factors
Laissy 2011[148]	Incorrect study design - narrative review
Lancellotti 2017[149]	Incorrect study design - narrative review
Lantelme 2019[150]	Incorrect prognostic factors
Larroche 2020[151]	Incorrect prognostic factor
Latsios 2010[153]	Incorrect outcomes
Leber 2013[154]	Incorrect prognostic factor
Lee 2020[156]	Incorrect analysis - unadjusted results only for prognostic factors matching protocol and sufficient studies with multivariate results for this prognostic factor
Lella 2015[157]	Incorrect population <50% HVD and not stratified
Lindsay 2015[159]	Incorrect prognostic factors
Liu 2017[160]	Incorrect study design - protocol only and no results published
Liu 2019[161]	Incorrect study design - narrative review
Maeno 2017[163]	Incorrect prognostic factor
Malahfji 2019[164]	Incorrect study design - narrative review
Mamane 2016[165]	Incorrect prognostic factor
Markowiak 2019[166]	Incorrect prognostic factor and outcomes
Marwan 2013[167]	Incorrect outcome
Masri 2016[168]	Incorrect prognostic factor
Masri 2016[169]	Incorrect population
Massaro 2016[170]	Incorrect outcome
Massera 2019[171]	Incorrect study design, prognostic factors and outcomes
Matsumoto 2014[172]	Incorrect prognostic factor
Matsushita 2020[173]	Incorrect prognostic factors and outcomes
Mehta 2017[174]	Incorrect study design - narrative review

Reference	Reason for exclusion
Mejean 2016[175]	Incorrect outcome and prognostic factors
Merten 2013[176]	Incorrect study design
Messika-Zeitoun 2004[177]	Incorrect population
Michelena 2015[178]	Incorrect study design - narrative review
Mistiaen 2004[179]	Incorrect prognostic factors and outcome
Mohty 2013[180]	Incorrect prognostic factors
Mojazi-Amiri 2013[181]	Incorrect study design - narrative review
Mok 2016[182]	Incorrect prognostic factors
Mordi 2015[183]	Incorrect population
Morosin 2017[184]	Incorrect prognostic factors
Mrsic 2019[185]	Incorrect study design - narrative review
Musa 2016[186]	Incorrect study design - narrative review
Musa 2016[10]	Incorrect prognostic factors
Musa 2017[188]	Incorrect analysis - unadjusted results only and sufficient studies with multivariate results for this prognostic factor
Myerson 2012[189]	Incorrect study design - narrative review
Mylotte 2014[192]	Incorrect prognostic factor
Nadjiri 2016[193]	Incorrect prognostic factor
Naoum 2017[194]	Incorrect study design - narrative review
Natarajan 2017[195]	Incorrect study design - narrative review
Nchimi 2018[197]	Systematic review - references checked
Neisius 2020[198]	Incorrect outcome
Nigri 2006[200]	Incorrect study design - narrative review
Nigri 2006[201]	Incorrect study design
Ochiai 1999[203]	Incorrect study design
Oh 2020[204]	Incorrect prognostic factors - none matching protocol
Okuno 2020[205]	Incorrect prognostic factors - none matching protocol
O'Neal 2015[202]	Incorrect population
Orme 2014[206]	Incorrect prognostic factors
Paknikar 2016[207]	Incorrect prognostic factor
Papanastasiou 2020[208]	Systematic review - references checked
Park 2014[209]	Incorrect outcomes
Park 2018[210]	Incorrect prognostic factor and outcome
Podlesnikar 2018[214]	Incorrect study design - narrative review
Pohle 2004[215]	Incorrect population
Pollari 2019[216]	Incorrect outcomes
Pollari 2020[217]	Incorrect prognostic factors and outcomes
Possner 2016[218]	Incorrect prognostic factors
Prabhakar 2020[219]	Narrative review - references checked
Pulignano 2017[220]	Incorrect study design - narrative review
Putra 2019[221]	Incorrect prognostic factor

Reference	Reason for exclusion
Quarto 2012[222]	Incorrect analysis - unadjusted results only and sufficient studies with multivariate results for this prognostic factor
Raggi 2011[223]	Incorrect population
Rajani 2014[224]	Incorrect study design - narrative review
Raju 2019[226]	Incorrect prognostic factors - none matching protocol
Ramana 2019[227]	Incorrect study design
Rangarajan 2016[228]	Incorrect population and prognostic factor
Reddy 2017[229]	Incorrect study design
Reinders 2015[230]	Incorrect outcomes, prognostic factors and insufficient reporting
Reinthaler 2015[231]	Incorrect prognostic factor
Revilla-Orodea 2016[232]	Incorrect population
Ribeiro 2016[233]	Incorrect study design
Rodrigues 2016[234]	Incorrect prognostic factors
Rodriguez-Olivares 2016[235]	Incorrect prognostic factor and outcome
Rosenhek 2000[236]	Incorrect prognostic factors
Rozenbaum 2019[238]	Incorrect prognostic factor
Rozenbaum 2020[237]	Incorrect prognostic factors - none matching protocol
Rys 2018[239]	Incorrect outcome
Saji 2016[240]	Incorrect prognostic factor
Sakrana 2016[241]	Incorrect outcome
Sales Mda 2014[242]	Incorrect prognostic factor
Sanati 2017[243]	Incorrect prognostic factor and outcomes
Schymik 2017[244]	Incorrect prognostic factors
Seiffert 2016[245]	Incorrect prognostic factor and outcomes
Seldrum 2019[246]	Insufficient reporting of prognostic variable definition for MR; incorrect prognostic factor and outcome for AR
Shah 2014[247]	Incorrect prognostic factor
Shen 2020[248]	Incorrect prognostic factors - none matching protocol
Shimizu 2015[249]	Incorrect population
Showkathali 2015[250]	Incorrect prognostic factor
Sigvardsen 2018[251]	Incorrect prognostic factor
Singh 2013[252]	Incorrect prognostic factors
Singh 2017[253]	Incorrect prognostic factors
Soulat 2017[254]	Incorrect study design and outcomes
Souza 2016[255]	Incorrect prognostic factor
Spaziano 2018[256]	Incorrect prognostic factor
Stahli 2015[257]	Incorrect prognostic factor and outcome
Stahli 2015[258]	Incorrect study design and prognostic factor
Staniloae 2019[259]	Incorrect study design
Steadman 2012[260]	Incorrect outcomes

Reference	Reason for exclusion
Stundl 2020[261]	No prognostic data
Suh 2019[262]	Incorrect prognostic factors - none matching protocol
Suh 2019[263]	Incorrect outcome
Szekely 2020[264]	Incorrect prognostic factors - none matching protocol
Szilveszter 2020[265]	Incorrect prognostic factors - none matching protocol
Takami 2016[266]	Incorrect prognostic factor
Takeda 2011[267]	Incorrect prognostic factors and insufficient reporting
Taniguchi 2020[268]	Incorrect prognostic factors and outcomes
Tokuda 2020[269]	Incorrect prognostic factors - none matching protocol
Treibel 2016[270]	Incorrect prognostic factors
Tsang 2012[271]	Incorrect population
Tsutsumi 2016[272]	Incorrect outcome
Tzemos 2008[273]	Incorrect population and prognostic factors
Uretsky 2020[274]	Incorrect prognostic factors and outcomes
Vahanian 2010[276]	Incorrect study design - narrative review
Valenti 2015[277]	Incorrect prognostic variable and outcome
Valkov 2016[278]	Incorrect study design - narrative review
van Kesteren 2017[280]	Incorrect prognostic factor
van Kesteren 2018[279]	Incorrect outcome
van Mourik 2019[281]	Incorrect prognostic factor
Velu 2019[282]	Incorrect prognostic factor
Watanabe 2015[283]	Incorrect prognostic factors
Weidemann 2009[284]	Insufficient reporting
Weissman 2009[285]	Incorrect study design - narrative review
Wenaweser 2011[286]	Incorrect prognostic factors
Wong 2013[287]	Incorrect population, outcome and prognostic factor
Yanagisawa 2017[288]	Incorrect prognostic factor
Yanagisawa 2019[289]	Incorrect prognostic factor and outcome
Yildirim 2007[290]	Incorrect study design - no follow-up of patient outcomes
Zamorano 2019[292]	Not in English language
Zhan 2020[293]	Incorrect prognostic factors: none listed in protocol
Zhang 2020[294]	Incorrect population - already had intervention
Zhu 2015[295]	Incorrect analysis - correlation only

Health Economic studies

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

None.

Appendix K – Research recommendations – full details

K.1 Severity of valvular regurgitation on cardiac MRI

K.1.1 Research recommendation

In adults with aortic or primary mitral regurgitation in whom the need for intervention is unclear after echocardiography, what is the prognostic value and cost effectiveness of cardiac MRI to assess the severity of valvular regurgitation?

K.1.1.1 Why this is important

Current practice is based on echocardiography, readily available and low-cost imaging modality with a long record of clinical use for assessment and follow-up of patient with heart valve disease and studies of outcomes underpinning timing of valve intervention. Cardiac MRI is a less readily available and more costly imaging modality, established for the assessment of cardiac chambers dimensions and function and tissue characterisation of the heart myocardium and cardiac masses. In these areas, cardiac MRI is demonstrated to have better accuracy then echocardiography. However, there are no studies of outcomes to underpin a role for cardiac MRI in the assessment of valve disease severity for mitral and aortic regurgitation and indeed for other types of heart valve disease. There are no studies of outcomes even for the use of MRI to determine timing of intervention based on parameters related to left ventricular dimensions and function, currently derived from echocardiography for heart valve disease. Maybe cardiac MRI could represent an appropriate or better alternative than echocardiography for the assessment of aortic and mitral regurgitation and consequences on the left ventricle in all cases or in cases where echocardiography is non-diagnostic for example because of poor window.

K.1.1.2 Rationale for research recommendation

Importance to 'patients' or the population	To provide an appropriate or better alternative than echocardiography for the assessment of aortic and primary mitral regurgitation and consequences on the left ventricle in all cases or in cases where echocardiography is non-diagnostic for example because of poor window.
Relevance to NICE guidance	Future NICE guidelines may recommend the use for cardiac MRI for follow-up of patients with mitral or aortic regurgitation or at least for a one-off assessment to confirm the need for intervention or the absence of it.
Relevance to the NHS	The introduction of cardiac MRI for those in whom the need for intervention is unclear after echocardiography may lead to significant increase in cost that, however, may be balanced by the benefit of accuracy and avoidance of adverse events due to delayed intervention.
National priorities	"Action on prevention" long term plan
Current evidence base	Limited multivariate evidence was identified. Further studies are needed to inform recommendations on cardiac MRI

Equality considerations	None identified

K.1.1.3 Modified PICO table

Population	Inclusion Adults aged 18 years and over with diagnosed heart valve disease requiring further tests after echocardiography to determine whether intervention is needed. It should be clear that the population represented is those in whom there was uncertainty about whether intervention was indicated Data will be stratified by the type of heart valve disease as follows: • aortic [including bicuspid] regurgitation • primary mitral regurgitation Exclusion • Children (aged <18 years) • Adults with congenital heart disease (excluding bicuspid aortic valves). • Adults with previous intervention for HVD (surgical or transcatheter).
Prognostic variable	**Primary mitral regurgitation** • Quantification of MR on cardiac MRI (regurgitant fraction in % or regurgitant volume in ml) Note that there are currently no accepted thresholds for severe MR based on these parameters on cardiac MRI, but the use of thresholds within the following ranges are suggested for investigation: • Regurgitant fraction, 30-50% • Regurgitant volume, 40-60 ml **Aortic regurgitation** • Quantification of AR on cardiac MRI (regurgitant fraction in % or regurgitant volume in ml) Note that there are currently no accepted thresholds for severe AR based on these parameters on cardiac MRI, but the use of thresholds within the following ranges are suggested for investigation: • Regurgitant fraction, 30-50% Regurgitant volume, 40-60 ml

Outcome	Indication for intervention based on prognosis for the following without intervention: • Mortality (1 and 5 years) • Hospital admission for heart failure or unplanned intervention (1 and 5 years) • Reduced cardiac function (echo parameters – LVEF) 1 and 5 years • Symptom onset or symptom worsening (e.g. that led to surgery being required) 1 and 5 years Indication for intervention based on predictors of the following post-operative outcomes: • Mortality (6 and 12 months) • Hospital admission for heart failure (6 and 12 months) • Reduced cardiac function (echo or cardiac MRI parameters – for example LVEF <50%) (6 and 12 months) • Return to normal LV volumes post-operatively based on echo or cardiac MRI as defined in the study (6 and 12 months) • >20% reduction in LV volume post-operatively based on echo or cardiac MRI (6 and 12 months)
Study design	Cohort adjusted for all key confounders
Timeframe	Long term
Additional information	None

K.2 LVEF on cardiac MRI in aortic or mitral regurgitation

K.2.1 Research recommendation

In adults with aortic or mitral regurgitation in whom the need for intervention is unclear after echocardiography, what is the prognostic value and cost effectiveness of left ventricular ejection fraction measured on cardiac MRI to assess the need for intervention?

K.2.1.1 Why this is important

Prognostic parameters that predict symptomatic deterioration, development of heart failure that may not be reversible following valve intervention or mortality inform the need for valve intervention in patients with asymptomatic severe heart valve disease to avoid poor outcome

K.2.1.2 Rationale for research recommendation

Importance to 'patients' or the population	To provide an appropriate or better alternative than echocardiography which will lead to a reduction in adverse events due to delayed intervention
Relevance to NICE guidance	Evidence for this prognostic factor may support specific recommendations on the prognostic

	value of left ventricular ejection fraction measured on cardiac MRI in these populations
Relevance to the NHS	The introduction of cardiac MRI for those in whom the need for intervention is unclear after echocardiography may lead to significant increase in cost that, however, may be balanced by the benefit of accuracy and avoidance of adverse events due to delayed intervention.
National priorities	"Action on prevention" long term plan
Current evidence base	No evidence was identified for this prognostic factor in these populations.
Equality considerations	None identified

K.2.1.3 Modified PICO table

Population	Inclusion Adults aged 18 years and over with diagnosed heart valve disease requiring further tests after echocardiography to determine whether intervention is needed. It should be clear that the population represented is those in whom there was uncertainty about whether intervention was indicated Data will be stratified by the type of heart valve disease as follows: • aortic [including bicuspid] regurgitation • primary mitral regurgitation • secondary mitral regurgitation Exclusion • Children (aged <18 years) • Adults with congenital heart disease (excluding bicuspid aortic valves). • Adults with previous intervention for HVD (surgical or transcatheter).
Prognostic variables	Left ventricular ejection fraction measured on cardiac MRI
Outcome	Indication for intervention based on prognosis for the following without intervention: • Mortality (1 and 5 years) • Hospital admission for heart failure or unplanned intervention (1 and 5 years) • Reduced cardiac function (echo parameters – LVEF) 1 and 5 years • Symptom onset or symptom worsening (e.g. that led to surgery being required) 1 and 5 years Indication for intervention based on predictors of the following post-operative outcomes: • Mortality (6 and 12 months)

	- Hospital admission for heart failure (6 and 12 months) - Reduced cardiac function (echo or cardiac MRI parameters – for example LVEF <50%) (6 and 12 months) - Return to normal LV volumes post-operatively based on echo or cardiac MRI as defined in the study (6 and 12 months) - >20% reduction in LV volume post-operatively based on echo or cardiac MRI (6 and 12 months)
Study design	Cohort study adjusted for all key confounders
Timeframe	Long term
Additional information	None

K.3 LVEF on cardiac MRI in aortic stenosis

K.3.1 Research recommendation

In adults with asymptomatic severe aortic stenosis what is the prognostic value and cost effectiveness of left ventricular ejection fraction measured on cardiac MRI to assess the need for intervention?

K.3.1.1 Why this is important

Prognostic parameters that predict symptomatic deterioration, development of heart failure that may not be reversible following valve intervention or mortality inform the need for valve intervention in patients with asymptomatic severe heart valve disease to avoid poor outcome

K.3.1.2 Rationale for research recommendation

Importance to ‘patients’ or the population	To provide an appropriate or better alternative than echocardiography
Relevance to NICE guidance	Additional evidence may support specific recommendations on the prognostic value of left ventricular ejection fraction measured on cardiac MRI in this populations
Relevance to the NHS	The introduction of cardiac MRI for those in whom the need for intervention is unclear after echocardiography may lead to an increase in cost that, however may be balanced by the benefit in accuracy and avoidance of adverse events due to delayed intervention
National priorities	“Action on prevention” long term plan
Current evidence base	The evidence base was very limited with only a few studies identified and uncertainty present in the results
Equality considerations	None identified

K.3.1.3 Modified PICO table

Population	<u>Inclusion</u> Adults aged 18 years and over with diagnosed asymptomatic severe aortic stenosis requiring

	further tests after echocardiography to determine whether intervention is needed. Exclusion • Children (aged <18 years) • Adults with congenital heart disease (excluding bicuspid aortic valves). • Adults with previous intervention for HVD (surgical or transcatheter).
Prognostic variables	Left ventricular ejection fraction measured on cardiac MRI
Outcome	Indication for intervention based on prognosis for the following without intervention: • Mortality (1 and 5 years) • Hospital admission for heart failure or unplanned intervention (1 and 5 years) • Reduced cardiac function (echo parameters – LVEF) 1 and 5 years • Symptom onset or symptom worsening (e.g. that led to surgery being required) 1 and 5 years Indication for intervention based on predictors of the following post-operative outcomes: • Mortality (6 and 12 months) • Hospital admission for heart failure (6 and 12 months) • Reduced cardiac function (echo or cardiac MRI parameters – for example LVEF <50%) (6 and 12 months) • Return to normal LV volumes post-operatively based on echo or cardiac MRI as defined in the study (6 and 12 months) • >20% reduction in LV volume post-operatively based on echo or cardiac MRI (6 and 12 months)
Study design	Cohort adjusted for all key confounders
Timeframe	Long term
Additional information	None

K.4 Cardiac MRI in tricuspid regurgitation

K.4.1 Research recommendation

In adults with asymptomatic severe tricuspid regurgitation what is the prognostic value and cost effectiveness of cardiac MRI for assessment of the right ventricle to assess the need for intervention?

K.4.1.1 Why this is important

Prognostic parameters that predict symptomatic deterioration, development of heart failure that may not be reversible following valve intervention or mortality inform the need for valve intervention in patients with asymptomatic severe heart valve disease to avoid poor outcome

K.4.1.2 Rationale for research recommendation

Importance to 'patients' or the population	To provide an appropriate or better alternative than echocardiography
Relevance to NICE guidance	Evidence may support recommendations on the prognostic value of MRI in this population.
Relevance to the NHS	The introduction of cardiac MRI for those in whom the need for intervention is unclear after echocardiography may lead to significant increase in cost that, however, may be balanced by the benefit in accuracy and avoidance of adverse events due to delayed intervention.
National priorities	"Action on prevention" long term plan
Current evidence base	One small study was identified that looked at the prognostic value of a reduced right ventricular ejection fraction on cardiac MRI to predict outcome in tricuspid regurgitation, which was not considered sufficient to base recommendations on
Equality considerations	None identified

K.4.1.3 Modified PICO table

Population	Inclusion Adults aged 18 years and over with diagnosed tricuspid regurgitation requiring further tests after echocardiography to determine whether intervention is needed. Exclusion • Children (aged <18 years) • Adults with congenital heart disease (excluding bicuspid aortic valves). • Adults with previous intervention for HVD (surgical or transcatheter).
Prognostic variables	Right ventricular ejection fraction on cardiac MRI
Outcome	Indication for intervention based on prognosis for the following without intervention: • Mortality (1 and 5 years) • Hospital admission for heart failure or unplanned intervention (1 and 5 years) • Reduced cardiac function (echo parameters – LVEF) 1 and 5 years • Symptom onset or symptom worsening (e.g. that led to surgery being required) 1 and 5 years Indication for intervention based on predictors of the following post-operative outcomes: • Mortality (6 and 12 months)

	• Hospital admission for heart failure (6 and 12 months) • Reduced cardiac function (echo or cardiac MRI parameters – for example LVEF <50%) (6 and 12 months) • Return to normal LV volumes post-operatively based on echo or cardiac MRI as defined in the study (6 and 12 months) • >20% reduction in LV volume post-operatively based on echo or cardiac MRI (6 and 12 months)
Study design	Cohort adjusted for all key confounders
Timeframe	Long term
Additional information	None