## D.2 Aortic stenosis – myocardial fibrosis on cardiac MRI

| Reference | Agoston-Coldea 2019[6] |
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| Study type and analysis | Prospective cohort pilot study<br>Multivariable Cox regression model |
| Number of participants and characteristics | Total n=52<br>LGE positive: 30<br>LGE negative: 22<br><br>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%)<br><br>**Inclusion criteria**<br>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<br><br>**Exclusion criteria**<br>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<br><br>**Values listed below are presented as mean (SD), median (IQR) or number (%)**<br><br>**Patient characteristics:**<br>Age: 66 (7.5) years<br>Male: 55.7%<br>Smoking: 36.5%<br>CAD: 32.6%<br>NYHA class ≥ III: 28.8%<br>Logistic EuroScore II: 3.8 (1.3-5.9)<br>Systolic blood pressure, mmHg: 132 (18.1)<br>Chronic obstructive lung disease: 11.5% |

| Reference | Agoston-Coldea 2019[6] |
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| | NT-proBNP, pg/mL: 1960 (170-9893)<br>Preserved LVEF: 73%<br><br>**Population source**: single site in Romania, between March 2016 and August 2018.<br>Consecutive sample, but 76/128 ineligible for inclusion |
| Prognostic variable | **Presence or absence of LGE on CMR imaging.**<br><br>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.<br>All CMR imaging examinations were performed by two experienced examiners, one cardiologist and one radiologist *blinded* to all clinical data.<br>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.<br>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.<br><br>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.<br><br>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.<br><br>Adjusted HR = 11.3 (95% CI 1.82–70.2) for LGE present vs LGE absent |

| Reference | Agoston-Coldea 2019[6] |
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| | 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:<br>1. Study participation LOW<br>2. Study attrition LOW<br>3. Prognostic factor measurement LOW<br>4. Outcome Measurement LOW<br>5. Study confounding LOW<br>6. Statistical analysis HIGH<br>7. Other risk of bias LOW<br>OVERALL RISK OF BIAS HIGH<br><br>Indirectness:<br>• Outcome – indirect outcome definition, a composite of events including some protocol outcomes<br>• Population – all having aortic valve replacement, so need for intervention already determined |

| Reference | Barone-Rochette 2014[22] |
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| Study type and analysis | Prospective cohort study<br><br>Multivariate Cox proportional hazards model.<br><br>Belgium |
| Number of participants and characteristics | N=154 undergoing surgical aortic valve replacement (AVR)<br>Late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR), n=44<br>No LGE on CMR, n=110<br><br>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] |
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| | 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.<br><br>**Inclusion criteria:**<br>>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.<br><br>**Exclusion criteria:**<br>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.<br><br>**Values listed below are presented as mean (SD) or number (%)**<br><br><u>LGE on CMR</u><br>• Age: 75 (9) years<br>• Male/female: 28/16 (64%/36%)<br>• Hypertension, 26 (59%)<br>• Hyperlipidaemia, 25 (57%)<br>• Smoking history:<br>  ○ Former smoker, 9 (21%)<br>  ○ Current smoker, 7 (16%)<br>• Diabetes, 15 (34%)<br>• Family history of coronary artery disease, 9 (20%)<br>• NYHA functional class III/IV, 13 (30%)<br>• Chest pain, 9 (21%)<br>• Syncope, 5 (11%)<br>• Chronic obstructive pulmonary disease, 8 (18%)<br>• Peripheral artery disease, 5 (11%) |

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

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

| Reference | Barone-Rochette 2014[22] |
|---|---|
| | • Age: 75 (9) years<br>• Male/female: 28/16 (64%/36%)<br>• Hypertension, 26 (59%)<br>• Hyperlipidaemia, 25 (57%)<br>• Smoking history:<br>  ○ Former smoker, 9 (21%)<br>  ○ Current smoker, 7 (16%)<br>• Diabetes, 15 (34%)<br>• Family history of coronary artery disease, 9 (20%)<br>• NYHA functional class III/IV, 13 (30%)<br>• Chest pain, 9 (21%)<br>• Syncope, 5 (11%)<br>• Chronic obstructive pulmonary disease, 8 (18%)<br>• Peripheral artery disease, 5 (11%)<br>• Stroke, 6 (14%)<br>• Prior percutaneous coronary intervention, 2 (5%)<br>• Glomerular filtration rate: 72 (25) ml/min/$m^2$<br>• Logistic EuroSCORE I: 7.6 (4.9)%<br>• STS score: 2.5 (1.4)%<br>• Atrial fibrillation, 5 (9%)<br>• Left bundle branch block, 6 (14%)<br>• Systolic blood pressure: 135 (20) mmHg<br>• Heart rate: 69 (13) bpm<br><br>• Aortic valve area: 0.70 (0.18) $cm^2$<br>• Indexed aortic valve area: 0.38 (0.09) $cm^2/m^2$<br>• Peak transvalvular aortic gradient: 77 (28) mmHg<br>• Mean transvalvular aortic gradient: 47 (18) mmHg<br>• Coronary artery disease, 12 (29%)<br>• Vessels affected by coronary disease: 1.9 (1.2) |

| Reference | Barone-Rochette 2014[22] |
|---|---|
| | • Indexed end-diastolic volume on CMR: 83 (27) ml/m$^2$<br>• Indexed end-systolic volume on CMR: 41 (28) ml/m$^2$<br>• Ejection fraction on CMR: 55 (18)%<br>• Indexed LV mass: 99 (31) g/m$^2$<br><br>**Population source:** patients matching inclusion criteria from a single institution in Belgium between February 2005 and November 2012. |
| Prognostic variable | LGE on CMR<br>No LGE on CMR (referent)<br><br>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.<br><br>CMR performed at median of 3 days (range, 0-180 days) prior to surgery. |
| Confounders | Multivariate Cox proportional hazards model.<br><br>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.<br><br>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.<br><br>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] |
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| Outcomes and effect sizes | **<u>All-cause mortality following surgical AVR</u>**<br>**HR 2.80 (95% CI 1.10 to 6.90, P=0.025) for LGE on CMR vs. no LGE on CMR**<br><br>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.<br><br>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).<br><br>No multivariate results were available for cardiovascular-related deaths or postoperative deaths within 30 days.<br><br>Median follow-up: 2.9 years (100% complete) in those receiving surgical AVR. |
| Comments | **<u>All-cause mortality following surgical AVR</u>**<br>Risk of bias:<br>1. Study participation — LOW<br>2. Study attrition — LOW<br>3. Prognostic factor measurement — LOW<br>4. Outcome Measurement — LOW<br>5. Study confounding — HIGH<br>6. Statistical analysis — VERY HIGH<br>7. Other risk of bias — LOW<br>OVERALL RISK OF BIAS — VERY HIGH<br><br>Indirectness:<br>• Population - all already scheduled to have AVR so population is not those where there is uncertainty about whether or not intervention is indicated<br>• 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] |
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| Study type and analysis | Prospective cohort study<br><br>Multivariate Cox proportional hazards analysis<br><br>Denmark |
| Number of participants and characteristics | N=78 (n=92 overall with cardiac MRI performed, but only n=78 had data for fibrosis)<br><br>Fibrosis on cardiac MRI, n=21<br>No fibrosis on cardiac MRI, n=57<br><br>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.<br><br>**Inclusion criteria:**<br>≥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.<br><br>**Exclusion criteria:**<br>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.<br><br>**Values listed below are presented as mean (SD) or number (%)**<br><u>Whole cohort of 92 patients – not limited to the 78 with data available for fibrosis on cardiac MRI</u><br>• Age: 74 (8) years<br>• Male/female: 52/40 (57%/43%)<br>• Coronary artery disease, 3 (3%)<br>• Hypertension, 63 (68%)<br>• Peripheral artery disease, 1 (1%)<br>• Diabetes mellitus, 12 (13%)<br>• Diuretics, 29 (32%) |

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

| Reference | Christensen 2017[57] |
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| | • RV end-systolic volume index on cardiac MRI: 26 (7) ml/m$^2$<br>• RV ejection fraction on cardiac MRI: 62 (7)%<br>• LV mass on cardiac MRI: 130 (36) g<br>• LV mass index on cardiac MRI: 69 (17) g/m$^2$<br>• Aortic stroke volume on cardiac MRI: 70 (18) ml<br>• Aortic stroke volume index on cardiac MRI: 38 (8) ml/m$^2$<br>• Aortic regurgitant fraction on cardiac MRI: 8 (6)%<br>• Fibrosis on cardiac MRI on cardiac MRI: 21/78 (27%)<br><br>**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<br>No fibrosis on cardiac MRI (referent)<br><br>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<br><br>Factors included in adjusted analysis: age, gender and aortic mean gradient<br><br>One of the pre-specified confounders included in analysis (age), but not the other (smoking). |
| Outcomes and effect sizes | **Unplanned hospital admissions (for atrial fibrillation, heart failure or acute coronary syndrome), aortic valve replacement (AVR) or death**<br>**HR 1.17 (95% CI 0.44 to 3.11) for fibrosis on cardiac MRI vs. no fibrosis on cardiac MRI**<br><br>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] |
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| | 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.<br><br>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**<br>Risk of bias:<br>1. Study participation HIGH<br>2. Study attrition LOW<br>3. Prognostic factor measurement LOW<br>4. Outcome Measurement HIGH<br>5. Study confounding HIGH<br>6. Statistical analysis HIGH<br>7. Other risk of bias LOW<br>OVERALL RISK OF BIAS VERY HIGH<br><br>Indirectness:<br>• Outcome – composite outcome of three separate outcomes listed in the protocol, rather than reporting them separately.<br>• 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] |
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| Study type and analysis | Prospective cohort study<br><br>Multivariate Cox proportional hazards regression<br><br>UK |
| Number of participants | N=143 |

| Reference | Dweck 2011[84] |
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| and characteristics | Midwall fibrosis based on late gadolinium enhancement (LGE) pattern on cardiac magnetic resonance (CMR), n=54<br>No LGE on CMR, n=49<br><br>Infarct pattern fibrosis based on LGE on CMR, n=40<br>No LGE on CMR, n=49<br><br>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.<br><br>**Inclusion criteria:**<br>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);<br><br>**Exclusion criteria:**<br>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.<br><br>**Values listed below are presented as mean (SD) or number (%)**<br><br><u>Midwall LGE</u><br>• Age: 70 (11) years<br>• Male/female: 39/15 (72%/28%)<br>• Atrial fibrillation, 10 (18%)<br>• Diabetes mellitus, 10 (19%)<br>• Hypertension, 28 (55%)<br>• Bicuspid aortic valve, 9 (17%)<br>• Documented coronary artery disease, 23 (42%)<br>  ○ 1-vessel, 9 (17%)<br>  ○ 2-vessel, 3 (6%) |

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

| Reference | Dweck 2011[84] |
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| | • ACE inhibitor, 24 (61%)<br>• Beta-blocker, 20 (49%)<br>• Statins, 33 (82%)<br>• Diuretic use, 16 (41%)<br>• Aortic valve area on CMR: 0.91 (0.26) $cm^2$<br>• Peak aortic valve gradient by echocardiography: 69 (16) mmHg<br>• Severe AS, 26 (65%)<br>• Ejection fraction: 44 (18)%<br>• Indexed left atrial volume, geometric mean (95% CI): 63.3 (57.1-70.2) $ml/m^2$<br>• Indexed left ventricular end-diastolic volume, geometric mean (95% CI): 101.4 (92.6-111.0) $ml/m^2$<br>• Indexed left ventricular mass, geometric mean (95% CI): 97.8 (90.9-105.2) $g/m^2$<br>• Right ventricular ejection fraction: 55 (14)%<br>• % LGE mass: 7.3<br><br><u>No LGE</u><br>• Age: 64 (16) years<br>• Male/female: 26/23 (53%/47%)<br>• Atrial fibrillation, 10 (21%)<br>• Diabetes mellitus, 12 (25%)<br>• Hypertension, 27 (56%)<br>• Bicuspid aortic valve, 14 (29%)<br>• Documented coronary artery disease, 18 (37%)<br>  ○ 1-vessel, 8 (16%)<br>  ○ 2-vessel, 1 (2%)<br>  ○ 3-vessel, 1 (2%)<br>  ○ Previous percutaneous coronary intervention, 5 (10%)<br>  ○ Previous coronary artery bypass grafting, 10 (20%)<br>• ACE inhibitor, 27 (56%)<br>• Beta-blocker, 27 (56%)<br>• Statins, 33 (67%) |

| Reference | Dweck 2011[84] |
|---|---|
| | • Diuretic use, 7 (15%)<br>• Aortic valve area on CMR: 1.05 (0.37) $cm^2$<br>• Peak aortic valve gradient by echocardiography: 70 (26) mmHg<br>• Severe AS, 26 (53%)<br>• Ejection fraction: 69 (13)%<br>• Indexed left atrial volume, geometric mean (95% CI): 58.9 (53.4-64.9) $ml/m^2$<br>• Indexed left ventricular end-diastolic volume, geometric mean (95% CI): 78.8 (72.1-86.2) $ml/m^2$<br>• Indexed left ventricular mass, geometric mean (95% CI): 92.6 (86.0-99.6) $g/m^2$<br>• Right ventricular ejection fraction: 58 (13)%<br>• % LGE mass: 0<br><br>**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<br>No LGE on CMR (referent)<br><br>Infarct pattern fibrosis based on LGE on CMR<br>No LGE on CMR (referent)<br><br>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.<br><br>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<br><br>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)**<br>**HR 5.35 (95% CI 1.16 to 24.56) for midwall LGE on CMR vs. no LGE on CMR**<br><br>**All-cause mortality – mixture of medical and surgically treated patients (AVR possibly adjusted for in model)**<br>**HR 2.56 (95% CI 0.48 to 13.64) for infarct LGE on CMR vs. no LGE on CMR**<br><br>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.<br>During follow-up, 72 patients (50%) had AVR (8% percutaneously), with no difference in the rate among the three groups.<br><br>No multivariate results were reported for cardiac mortality.<br><br>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.<br><br>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)**<br><br>Midwall LGE vs. no LGE<br>Risk of bias:<br>1. Study participation — LOW<br>2. Study attrition — LOW<br>3. Prognostic factor measurement — LOW<br>4. Outcome Measurement — LOW<br>5. Study confounding — HIGH<br>6. Statistical analysis — VERY HIGH<br>7. Other risk of bias — LOW |

| Reference | Dweck 2011[84] |
|---|---|
| | OVERALL RISK OF BIAS VERY HIGH<br><br>Indirectness:<br>• 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<br>• Prognostic factor – provides results separately for two different types of LGE on CMR, rather than as one combined result.<br>• Outcome – includes those with and without surgery during follow-up, whereas ideally aimed to look at results for non-operative and postoperative mortality separately<br>• 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.<br><br><u>Infarct LGE vs. no LGE</u><br>Risk of bias:<br>1. Study participation LOW<br>2. Study attrition LOW<br>3. Prognostic factor measurement LOW<br>4. Outcome Measurement LOW<br>5. Study confounding HIGH<br>6. Statistical analysis VERY HIGH<br>7. Other risk of bias LOW<br>OVERALL RISK OF BIAS VERY HIGH<br><br>Indirectness:<br>• 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<br>• Prognostic factor – provides results separately for two different types of LGE on CMR, rather than as one combined result.<br>• Outcome – includes those with and without surgery during follow-up, whereas ideally aimed to look at results for non-operative and postoperative mortality separately<br>• 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<br><br>Multivariate Cox regression model<br><br>UK, Germany, USA, Canada and South Korea |
| Number of participants and characteristics | N=440<br>Late gadolinium enhancement (LGE) on CMR, n=220<br>No LGE on CMR, n=220<br><br>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.<br><br>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%).<br><br>**Inclusion criteria:**<br>Severe AS scheduled for aortic valve intervention.<br><br>**Exclusion criteria:**<br>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.<br><br>**Values listed below are presented as mean (SD) or number (%)**<br><br>• Age: 69.67 (10.11) years<br>• Male/female: 259/181 (59%/41%)<br>• Body mass index: 27.60 (5.06) kg/$m^2$<br>• Body surface area: 1.85 (0.24) $m^2$<br>• Hypertension, 280 (64%) |

| Reference | Everett 2020[88] |
|---|---|
| | • Diabetes mellitus, 93 (21%)<br>• Atrial fibrillation, 56 (13%)<br>• Previous myocardial infarction, 38 (9%)<br>• Coronary artery disease, 168 (38%)<br>• NYHA functional class III/IV, 157 (36%)<br>• Systolic blood pressure: 130.7 (19.84) mmHg<br>• Diastolic blood pressure: 72.67 (12.04) mmHg<br>• 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.<br>• 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.<br><br>• Peak aortic jet velocity: 4.46 (0.80) m/s<br>• Peak aortic valve gradient: 81.99 (29.68) mmHg<br>• Mean aortic valve gradient: 49.66 (18.82) mmHg<br>• Aortic valve area: 0.73 (0.25) $cm^2$<br>• Indexed aortic valve area: 0.40 (0.13) $cm^2/m^2$<br>• Valvuloarterial impedance: 3.92 (1.12) $mmHg/ml/m^2$<br>• Bicuspid aortic valve, 144 (33%)<br><br>• Indexed LV end-diastolic volume: 78.33 (28.30) $ml/m^2$<br>• 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.<br>• Indexed LV stroke volume: 49 (13.49) $ml/m^2$<br>• LV ejection fraction: 66 (16.37)%<br>• LV ejection fraction <50%, 71 (16%)<br>• LV mass index: 93.33 (32.31) $g/m^2$<br>• Indexed RV end-diastolic volume: 65 (18.13) $ml/m^2$<br>• 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.<br>• Indexed RV stroke volume: 41.33 (10.69) $ml/m^2$ |

| Reference | Everett 2020[88] |
|---|---|
| | • RV ejection fraction: 64 (10.9)%<br>• Indexed left atrial volume: 53.33 (23.1) ml/$m^2$<br>• LGE, 220 (50%)<br><br>**Population source:** patients matching inclusion criteria from multiple prospective observational cohorts (10 centres across Europe, North America and Asia). |
| Prognostic variable | LGE on CMR<br>No LGE on CMR (referent)<br><br>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.<br><br>Variables with a significant association on univariate analysis were included in the multivariate model.<br><br>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.<br><br>Age was the confounder prespecified in the protocol for this outcome and has been included in the multivariate model. |
| Outcomes and effect sizes | **All-cause mortality following aortic valve intervention**<br>**HR 1.233 (95% CI 0.663 to 2.293) for LGE on CMR vs. no LGE on CMR**<br><br>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.<br><br>No multivariate results were provided for cardiovascular mortality.<br><br>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 | **All-cause mortality following aortic valve intervention**<br><br>LGE vs. no LGE on CMR<br>Risk of bias:<br>1. Study participation — LOW<br>2. Study attrition — LOW<br>3. Prognostic factor measurement — HIGH<br>4. Outcome Measurement — LOW<br>5. Study confounding — LOW<br>6. Statistical analysis — HIGH<br>7. Other risk of bias — LOW<br>OVERALL RISK OF BIAS — VERY HIGH<br><br>Indirectness:<br>• 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<br><br>Germany |
| Number of participants and characteristics | N=58 (only 46 had data for CMR fibrosis at baseline)<br><br>Mild fibrosis on cardiac magnetic resonance (CMR) imaging, n= not reported<br>No fibrosis on CMR, n= not reported<br><br>Severe fibrosis on CMR, n= not reported<br>No fibrosis on CMR, n= not reported<br><br>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.<br><br>**Inclusion criteria:**<br>Isolated symptomatic severe AS (symptoms one exertion and aortic valve area <1.0 $cm^2$).<br><br>**Exclusion criteria:**<br>Prior myocardial infarction; significant coronary artery disease (degree of stenosis >50%); prior heart surgery; malignant cancer; other valvulopathies > stage I.<br><br>**Values listed below are presented as mean (SD) or number (%)**<br>• Age: 68.3 (8.2) years<br>• Male/female: 35/23 (60.3%/39.7%)<br>• Body mass index: 28.9 (4.0) $kg/m^2$<br>• Systolic blood pressure: 125.4 (19.1) mmHg<br>• Diastolic blood pressure: 74.8 (10.7) mmHg<br>• NYHA functional class:<br>  ○ II, 8 (13.8%)<br>  ○ III, 38 (65.5%)<br>  ○ IV, 12 (20.7%) |

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

| Reference | Herrmann 2018[118] |
|---|---|
| | • LV mass on CMR: 194.1 (64.9) g<br><br>**Population source:** consecutive patients matching inclusion criteria from a single hospital between March 2006 and February 2007. |
| Prognostic variable | Mild fibrosis on CMR<br>No fibrosis on CMR (referent)<br><br>Severe fibrosis on CMR<br>No fibrosis on CMR (referent)<br><br>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.<br><br>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.<br><br>Factors included in adjusted analysis:<br>• Model 1: age, sex and CMR fibrosis grading<br>• Model 2: EuroSCORE and CMR fibrosis grading<br><br>Two different adjusted models were reported. Both were extracted as they contain different variables.<br><br>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**<br><br>Mild fibrosis vs. no fibrosis on CMR<br>• **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<br>• **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<br><br>Severe fibrosis vs. no fibrosis on CMR<br>• **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<br>• **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<br><br>Number of deaths during follow-up was not reported either combined or separately for the individual prognostic groups.<br><br>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.<br><br>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**<br><br>Mild fibrosis vs. no fibrosis on CMR<br>Risk of bias:<br>1. Study participation LOW<br>2. Study attrition LOW<br>3. Prognostic factor measurement HIGH<br>4. Outcome Measurement LOW<br>5. Study confounding LOW |

| Reference | Herrmann 2018[118] |
|---|---|
| | 6. Statistical analysis HIGH<br>7. Other risk of bias LOW<br>OVERALL RISK OF BIAS VERY HIGH<br><br>Indirectness:<br>• 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.<br>• Prognostic factor – specific severity of fibrosis on CMR compared with no fibrosis, rather than comparing any fibrosis with no fibrosis on CMR.<br><br><u>Severe fibrosis vs. no fibrosis on CMR</u><br>Risk of bias:<br>1. Study participation LOW<br>2. Study attrition LOW<br>3. Prognostic factor measurement HIGH<br>4. Outcome Measurement LOW<br>5. Study confounding LOW<br>6. Statistical analysis HIGH<br>7. Other risk of bias LOW<br>OVERALL RISK OF BIAS VERY HIGH<br><br>Indirectness:<br>• 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.<br>• 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<br><br>Multivariate Cox proportional hazard regression analysis<br><br>South Korea |
| Number of participants and characteristics | N=43<br>Diffuse myocardial fibrosis on pre-aortic valve replacement (AVR) cardiac magnetic resonance (CMR) imaging, n=30<br>Normal myocardium on pre-AVR CMR, n=13<br><br>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.<br><br>**Inclusion criteria:**<br>Severe AS scheduled for isolated AVR (without coronary artery bypass grafting).<br><br>**Exclusion criteria:**<br>≥moderate degree of other valve disease types; contraindications to CMR; prior cardiac surgery or myocardial infarction; patients where T1 mapping was not performed.<br><br>**Values listed below are presented as mean (SD) or number (%)**<br><br>• Age: 65.9 (8.1) years<br>• Male/female: 24/19 (55.8%/44.2%)<br>• Hypertension, 24 (55.8%)<br>• Diabetes mellitus, 7 (16.3%)<br>• Dyslipidaemia, 9 (20.9%)<br>• Atrial fibrillation, 7 (16.3%)<br>• Prior percutaneous coronary intervention, 3 (7.0%)<br>• Bicuspid aortic valve, 19 (44.2%)<br>• Current smoker, 3 (7.0%) |

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| | • EuroSCORE II: 1.50 (0.87)%<br>• Systolic blood pressure: 121.0 (18.3) mmHg<br>• Diastolic blood pressure: 71.2 (10.4) mmHg<br>• NYHA functional class: 2.1 (0.8)<br>• Chest pain, 12 (27.9%)<br>• Syncope, 6 (14.0%)<br><br>• Haemoglobin: 13.6 (1.7) g/dL<br>• Haematocrit: 40.3 (4.7)%<br>• Estimated glomerular filtration rate: 82.2 (14.6) ml/min/1.73 $m^2$<br><br>• Aortic valve Vmax, pre-AVR: 4.5 (0.8) m/s<br>• Aortic valve mean gradient, pre-AVR: 50.4 (17.3) mmHg<br>• Aortic valve area index, pre-AVR: 0.45 (0.13) $cm^2/m^2$<br>• Aortic valve Vmax, post-AVR: 2.4 (0.5) m/s<br>• Aortic valve mean gradient, post-AVR: 11.6 (6.4) mmHg<br>• Aortic valve area index, post-AVR: 1.05 (0.28) $cm^2/m^2$<br><br>**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<br>Normal myocardium on pre-AVR CMR (referent)<br><br>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. |
| Confounders | Multivariate Cox proportional hazard regression model with backward selection analysis used for univariate markers with P-values <0.100. |

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| | 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.<br><br>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**<br>**HR 5.516 (95% CI 1.031 to 29.508) for diffuse myocardial fibrosis vs. normal myocardium on pre-AVR CMR**<br><br>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.<br><br>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.<br><br>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**<br>Risk of bias:<br>1. Study participation — LOW<br>2. Study attrition — HIGH<br>3. Prognostic factor measurement — LOW<br>4. Outcome Measurement — LOW<br>5. Study confounding — HIGH<br>6. Statistical analysis — HIGH<br>7. Other risk of bias — LOW<br>OVERALL RISK OF BIAS — VERY HIGH<br><br>Indirectness:<br>• Population – all already scheduled for AVR so does not appear to be uncertainty as to whether there is an indication for intervention<br>• 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<br><br>Multivariate Cox regression analysis<br><br>South Korea |
| Number of participants and characteristics | N=127<br>Presence of late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR) imaging, n=41<br>Absence of LGE on CMR, n=86<br><br>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.<br><br>**Inclusion criteria:**<br>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<br><br>**Exclusion criteria:**<br>≥moderate degree of other valve disease; other medical conditions with life expectancy <1 year; uninterpretable images; lost to follow-up.<br><br>**Values listed below are presented as mean (SD) or number (%)**<br><br>• Age: 68.8 (9.2) years<br>• Male/female: 63/64 (49.6%/50.4%)<br>• Body surface area: 1.67 (0.15) $m^2$<br>• Hypertension, 84 (66.1%)<br>• Diabetes mellitus, 34 (26.8%) |

| Reference | Lee 2018[155] |
|---|---|
| | • Hyperlipidaemia, 36 (28.3%)<br>• Atrial fibrillation, 15 (11.8%)<br>• Prior coronary revascularisation, 17 (13.4%)<br>• EuroSCORE II: 1.58 (0.99)%<br>• Systolic blood pressure: 130.2 (18.9) mmHg<br>• Diastolic blood pressure: 70.9 (10.8) mmHg<br>• Heart rate: 66.6 (12.4) bpm<br>• Any typical AS symptoms, 68 (54.5%)<br>  ○ Dyspnoea (NYHA class II-IV), 62 (48.8%)<br>  ○ Chest pain, 33 (26.0%)<br>  ○ Syncope or pre-syncope, 16 (12.6%)<br>• Renin-angiotensin system blocker, 62 (48.8%)<br>• Beta-blocker, 43 (44.9%)<br>• Calcium-channel blocker, 31 (24.4%)<br>• Diuretics, 33 (26.0%)<br><br>• LV end-diastolic diameter: 49.7 (6.3) mm<br>• LV end-systolic diameter: 31.4 (7.4) mm<br>• Interventricular septal thickness: 11.3 (2.1) mm<br>• Posterior wall thickness: 11.0 (2.0) mm<br>• LV ejection fraction: 60.1 (9.7)%<br>• Left atrial diameter: 44.3 (6.8) mm<br>• E velocity: 0.71 (0.26) m/s<br>• e' velocity at septal annulus: 4.4 (1.4) cm/s<br>• E/e': 17.6 (8.4)<br>• Transaortic peak velocity: 4.4 (0.8) m/s<br>• Transaortic mean gradient: 48.0 (19.3) mmHg<br>• Aortic valve area: 0.82 (0.25) $cm^2$<br>• Severe AS, 79 (62.2%) |

| Reference | Lee 2018[155] |
|---|---|
| | • LV end-diastolic volume on CMR: 99.1 (34.5) ml/$m^2$<br>• LV end-systolic volume on CMR: 41.6 (30.2) ml/$m^2$<br>• LV ejection fraction on CMR: 61.8 (14.1)%<br>• LV mass index on CMR: 96.5 (35.5) g/$m^2$<br>• Presence of LGE on CMR, 41 (32.3%)<br>• % LGE mass on CMR: 5.2 (4.8)<br>• Native myocardial T1 value on CMR: 1232 (53) ms<br><br>**Population source:** consecutive patients matching inclusion criteria between October 2011 and November 2015 at a single site. |
| Prognostic variable | Presence of LGE on CMR<br>Absence of LGE on CMR (referent)<br><br>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<br><br>Factors included in adjusted analysis: EuroSCORE II, prior use of diuretics, presence of LGE on CMR and being within highest native T1 value tertile.<br><br>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. |
| Outcomes and effect sizes | **All-cause mortality and unexpected hospitalisation for heart failure during follow-up – mixture of those that received AVR and those that did not**<br>**HR 1.56 (95% CI 1.05 to 4.37) for presence of LGE vs. absence of LGE on CMR** |

| Reference | Lee 2018[155] |
|---|---|
| | 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).<br><br>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.<br><br>Median (IQR) follow-up: 27.9 (16.4-36.5) months |
| Comments | **All-cause mortality and unexpected hospitalisation for heart failure during follow-up – mixture of those that received AVR and those that did not**<br>Risk of bias:<br>1. Study participation — LOW<br>2. Study attrition — LOW<br>3. Prognostic factor measurement — LOW<br>4. Outcome Measurement — LOW<br>5. Study confounding — HIGH<br>6. Statistical analysis — HIGH<br>7. Other risk of bias — LOW<br>OVERALL RISK OF BIAS — VERY HIGH<br><br>Indirectness:<br>• 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.<br>• 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.<br>• 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<br><br>Multivariate Cox proportional hazards model<br><br>UK |
| Number of participants and characteristics | N=674 (note, only 613 had data available for LV myocardial scar assessment)<br>LV myocardial scar present on cardiac magnetic resonance (CMR) imaging – late gadolinium enhancement (LGE) present, n=341<br>No LV myocardial scar on CMR – LGE absent, n=272<br><br>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.<br>Median time from CMR to surgical AVR was 44 days (IQR, 11-103 days) and to transcatheter AVR was 13 days (1-61 days).<br><br>**Inclusion criteria:**<br>>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.<br><br>**Exclusion criteria:**<br>Previous valve intervention; uninterpretable image quality; insufficient demographic data; those referred that underwent only medical management.<br><br>**Values listed below are presented as mean (SD) or number (%)**<br><br><u>LGE on CMR (myocardial scar)</u><br>• Age, median (IQR): 74.3 (14.6) years<br>• Intervention:<br>  ○ Surgical AVR, 194 (56.9%)<br>  ○ Transcatheter AVR, 147 (43.1%)<br>• Male/female: 248/93 (72.7%/27.3%)<br>• Body mass index: 27.8 (5.1) $kg/m^2$ |

| Reference | Musa 2018[187] |
|---|---|
| | • Atrial fibrillation, 49 (14.4%)<br>• Diabetes mellitus, 77 (22.6%)<br>• Hypertension, 184 (54.0%)<br>• Systolic blood pressure: 133.4 (20.3) mmHg<br>• Diastolic blood pressure: 72.2 (11.8) mmHg<br>• Bicuspid aortic valve, 80 (23.5%)<br>• Known coronary artery disease, 123 (36.1%)<br>• No previous percutaneous coronary intervention/coronary artery bypass grafting, 260 (76.2%)<br>• Previous percutaneous coronary intervention, 38 (11.1%)<br>• Previous coronary artery bypass grafting, 31 (9.1%)<br>• History of myocardial infarction, 58 (17.0%)<br>• STS Mortality Risk score, median (IQR): 1.74 (1.79)%<br>• EuroSCORE II: 1.87 (2.85)%<br>• NYHA functional class:<br>  ○ I, 33 (9.7%)<br>  ○ II, 138 (40.5%)<br>  ○ III, 127 (37.2%)<br>  ○ IV, 10 (2.9%)<br>• ACE inhibitor or angiotensin-receptor blocker, 139 (40.8%)<br>• Beta-blocker, 130 (38.1%)<br>• Aldosterone antagonist, 21 (61.6%)<br>• Statin, 224 (65.7%)<br><br>• Mean aortic valve gradient, median (IQR): 46.0 (19.0) mmHg<br>• Peak aortic valve gradient, median (IQR): 78.0 (30.0) mmHg<br>• Aortic valve area, median (IQR): 0.70 (0.21) $cm^2$<br>• Indexed aortic valve area, median (IQR): 0.41 (0.13) $cm^2/m^2$<br>• Estimated pulmonary artery systolic pressure:<br>  ○ Normal, 159 (46.6%)<br>  ○ Moderate (31-55 mmHg), 43 (12.6%) |

| Reference | Musa 2018[187] |
|---|---|
| | ○ Severe (>55 mmHg), 16 (4.7%)<br><br>• LV end-diastolic volume index on CMR, median (IQR): 85.4 (33.4) ml/m$^2$<br>• LV stroke volume index on CMR, median (IQR): 46.0 (14.9) ml/m$^2$<br>• LV ejection fraction on CMR, median (IQR): 58.0 (21.0)%<br>• Maximal wall thickness on CMR, median (IQR): 14.0 (4.0) mm<br>• LV mass index on CMR, median (IQR): 87.1 (31.3) g/m$^2$<br>• RV end-diastolic volume index on CMR, median (IQR): 68.5 (22.5) ml/m$^2$<br>• RV ejection fraction on CMR, median (IQR): 63.8 (15.0)%<br>• Indexed left atrial volume on CMR, median (IQR): 53.3 (24.4) ml/m$^2$<br>• Aortic valve regurgitant fraction on CMR, median (IQR): 8.9 (16.2)%<br>• Valvuloarterial impedance on CMR, median (IQR): 3.93 (1.3)<br>• LGE pattern:<br>○ Non-infarct, 222 (65.1%)<br>○ Infarct, 119 (34.9%)<br>• LGE mass on CMR, median (IQR): 2.72 (3.95)%<br><br><u>No LGE on CMR (no myocardial scar)</u><br>• Age, median (IQR): 75.0 (14.5) years<br>• Intervention:<br>○ Surgical AVR, 176 (64.7%)<br>○ Transcatheter AVR, 96 (35.3%)<br>• Male/female: 148/124 (54.4%/45.6%)<br>• Body mass index: 27.3 (4.8) kg/m$^2$<br>• Atrial fibrillation, 28 (10.3%)<br>• Diabetes mellitus, 58 (21.3%)<br>• Hypertension, 155 (57.0%)<br>• Systolic blood pressure: 137.3 (20.2) mmHg<br>• Diastolic blood pressure: 74.0 (11.8) mmHg<br>• Bicuspid aortic valve, 53 (19.4%) |

| Reference | Musa 2018[187] |
|---|---|
| | • Known coronary artery disease, 74 (27.2%)<br>• No previous percutaneous coronary intervention/coronary artery bypass grafting, 220 (80.9%)<br>• Previous percutaneous coronary intervention, 16 (5.9%)<br>• Previous coronary artery bypass grafting, 22 (8.1%)<br>• History of myocardial infarction, 11 (4.0%)<br>• STS Mortality Risk score, median (IQR): 1.76 (1.69)%<br>• EuroSCORE II: 1.64 (1.69)%<br>• NYHA functional class:<br>  ○ I, 47 (17.3%)<br>  ○ II, 90 (33.1%)<br>  ○ III, 98 (36.0%)<br>  ○ IV, 8 (2.9%)<br>• ACE inhibitor or angiotensin-receptor blocker, 107 (39.3%)<br>• Beta-blocker, 92 (33.8%)<br>• Aldosterone antagonist, 11 (4.0%)<br>• Statin, 162 (59.6%)<br><br>• Mean aortic valve gradient, median (IQR): 46.0 (17.0) mmHg<br>• Peak aortic valve gradient, median (IQR): 79.5 (30.0) mmHg<br>• Aortic valve area, median (IQR): 0.70 (0.17) $cm^2$<br>• Indexed aortic valve area, median (IQR): 0.40 (0.13) $cm^2/m^2$<br>• Estimated pulmonary artery systolic pressure:<br>  ○ Normal, 138 (50.7%)<br>  ○ Moderate (31-55 mmHg), 30 (11.0%)<br>  ○ Severe (>55 mmHg), 11 (4.0%)<br><br>• LV end-diastolic volume index on CMR, median (IQR): 73.3 (23.1) $ml/m^2$<br>• LV stroke volume index on CMR, median (IQR): 45.8 (14.2) $ml/m^2$<br>• LV ejection fraction on CMR, median (IQR): 64.0 (12.0)%<br>• Maximal wall thickness on CMR, median (IQR): 13.0 (3.0) mm |

| Reference | Musa 2018[187] |
|---|---|
| | • LV mass index on CMR, median (IQR): 74.9 (28.5) g/m$^2$<br>• RV end-diastolic volume index on CMR, median (IQR): 66.8 (19.8) ml/m$^2$<br>• RV ejection fraction on CMR, median (IQR): 65.0 (11.0)%<br>• Indexed left atrial volume on CMR, median (IQR): 51.4 (25.4) ml/m$^2$<br>• Aortic valve regurgitant fraction on CMR, median (IQR): 7.7 (12.2)%<br>• Valvuloarterial impedance on CMR, median (IQR): 3.98 (1.5)<br><br>**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<br>No LV myocardial scar on CMR – LGE absent (referent)<br><br>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.<br><br>Factors included in adjusted analysis:<br>• **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.<br>• **Cardiovascular mortality:** Gender, previous coronary artery disease, LV ejection fraction on CMR, atrial fibrillation, age and presence of LGE (myocardial scar)<br><br>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.<br><br>Age was the only confounder listed for postoperative mortality and this has been included in the multivariate model. |

| Reference | Musa 2018[187] |
|---|---|
| Outcomes and effect sizes | **<u>All-cause mortality following AVR</u>**<br>**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)<br><br>**<u>Cardiovascular mortality following AVR</u>**<br>**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)<br><br>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.<br><br>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.<br><br>Median (IQR) follow-up: 3.6 (2.6-5.9) years. |
| Comments | **<u>All-cause mortality following AVR</u>**<br>Risk of bias:<br>1. Study participation — LOW<br>2. Study attrition — LOW<br>3. Prognostic factor measurement — HIGH<br>4. Outcome Measurement — LOW<br>5. Study confounding — LOW<br>6. Statistical analysis — LOW<br>7. Other risk of bias — LOW<br>OVERALL RISK OF BIAS — HIGH<br><br>Indirectness:<br>• Population – all included in analysis underwent AVR so already considered to be an indication for intervention. |

| Reference | Musa 2018[187] |
|---|---|
| | **Cardiovascular mortality following AVR**<br>Risk of bias:<br>1. Study participation LOW<br>2. Study attrition LOW<br>3. Prognostic factor measurement HIGH<br>4. Outcome Measurement LOW<br>5. Study confounding LOW<br>6. Statistical analysis LOW<br>7. Other risk of bias LOW<br>OVERALL RISK OF BIAS HIGH<br><br>Indirectness:<br>• 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<br><br>Multivariate logistic regression analysis<br><br>India |
| Number of participants and characteristics | N=109<br>Late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR) imaging, n=46<br>No LGE on CMR, n=63<br><br>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%).<br><br>**Inclusion criteria:** |

| Reference | Rajesh 2017[225] |
|---|---|
| | Adults with severe AS (indexed aortic valve area ≤0.6 $cm^2/m^2$ on echocardiography); CMR performed; CMR artefacts present<br><br>**Exclusion criteria:**<br>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.<br><br>**Values listed below are presented as mean (SD) or number (%)**<br><br><u>LGE on CMR (fibrosis present)</u><br>• Age: 58.7 (12.2) years<br>• Male/female: 27/19 (58.7%/41.3%)<br>• NYHA class I/II, 34 (73.9%)<br>• NYHA class III/IV, 11 (26.1%)<br>• Smoker, 6 (13%)<br>• Chronic obstructive pulmonary disease, 9 (19.5%)<br>• Angiographic coronary artery disease, 20 (43.4%)<br>• Chronic kidney disease, 3 (6.5%)<br>• Diabetes mellitus, 5 (10.8%)<br>• Hypertension, 24 (52.1%)<br>• Simpsons ejection fraction: 52.8 (12.4)%<br>• LV mass on CMR: 149.2 (28.4) g<br>• Aortic velocity time integral: 93.6 (10.2) cms<br>• Peak aortic velocity: 4.0 (0.5) m/s<br>• Peak systolic gradient: 67.4 (20.1) mmHg<br>• Mean gradient: 42.4 (13.2) mmHg<br>• Valvuloarterial impedance: 4.36 (1.5) $mmHg/m^2/ml$<br>• Indexed end-diastolic volume: 84 (20.4) $ml/m^2$<br><br><u>No LGE on CMR (no fibrosis)</u><br>• Age: 56.3 (12.7) years<br>• Male/female: 36/27 (57.1%/42.9%) |

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

| Reference | Rajesh 2017[225] |
|---|---|
| | 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<br><br>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**<br>**OR 1.68 (95% CI 0.60 to 4.60) for LGE on CMR (fibrosis) vs. no LGE on CMR (no fibrosis)**<br><br>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.<br><br>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.<br><br>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**<br>Risk of bias:<br>1. Study participation — LOW<br>2. Study attrition — HIGH<br>3. Prognostic factor measurement — LOW<br>4. Outcome Measurement — HIGH<br>5. Study confounding — LOW<br>6. Statistical analysis — VERY HIGH<br>7. Other risk of bias — LOW<br>OVERALL RISK OF BIAS — VERY HIGH<br><br>Indirectness: |

| Reference | Rajesh 2017[225] |
|---|---|
| | • 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.<br>• 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. |