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	**All-cause mortality following aortic valve intervention** **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	**All-cause mortality following aortic valve intervention** LVEF <50% vs. LVEF ≥50% 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 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%)

	• 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.

	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** **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	**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: • 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: ○ Never smoked, 102 (53.7%)

Reference	Lindsay 2016[158]
	○ 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%) ○ Symptoms at rest, 15 (7.9%)

Reference	Lindsay 2016[158]
	○ 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: ○ Yes, 82 (30.1%)

Reference	Lindsay 2016[158]
	○ 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	**All-cause mortality following TAVI** LVEF 30-49% vs. LVEF ≥50% on CMR **HR 1.19 (95% CI 0.69 to 2.04, P=0.533) for LVEF 30-49% on CMR vs. LVEF ≥50% on CMR** LVEF <30% vs. LVEF ≥50% on CMR **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	**All-cause mortality following TAVI** LVEF 30-49% vs. LVEF ≥50% on CMR 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.