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

Reference	Akodad 2018[8]
Study type and analysis	Prospective cohort study Multivariate logistic regression France
Number of participants and characteristics	N=118 (total of n=346 in paper, separated into two groups based on generation of TAVI valve received – useable results only provided for group 1 with first generation TAVI valves, which were Corevalve and Sapien XT valves) Calcium score >6,000 Hounsfield units (HU), n= not reported Calcium score ≤6,000 HU, n= not reported

Reference	Akodad 2018[8]

	Patients undergoing TAVI for aortic stenosis (AS). >50% were symptomatic (≥3 NYHA class) and mean aortic valve gradient was consistent with severe AS. Therefore, likely includes some with symptomatic severe AS, though the proportion is not clear. Population may therefore not fully represent the target population of the review.
	
	Inclusion criteria:
	Patients that underwent TAVI for AS.
	
	Exclusion criteria:
	None reported.
	
	Values listed below are presented as mean (SD) or number (%)
	
	<u>Those that received first generation valves in the study (Corevalve and Sapien XT) – no useable results for other group so not reported</u>
	• Age: 83.2 (6.4) years
	• Male/female: 52/66 (44%/56%)
	• Euroscore 1: 20.1 (11.4)
	• Euroscore 2: NA
	• Body mass index: 26.6 (5.4) kg/m^2
	• Chronic renal failure, 52. (44.1%)
	• Hypertension, 89 (75.4%)
	• Dyslipidaemia, 35 (29.7%)
	• Diabetes mellitus, 34 (28.8%)
	• Coronary artery disease, 59 (50.0%)
	• Peripheral arterial disease, 14 (11.9%)
	• NYHA ≥3, 60 (50.9%)
	• Mean aortic valve gradient: 48.9 (16.1) mmHg
	• LV ejection fraction: 51.9 (12.6)%
	• Main access site:
	  ○ Transfemoral, 108 (91.5%)
	  ○ Transcarotid, 1 (0.9%)
	  ○ Subclavian, 9 (7.6%)

Reference	Akodad 2018[8]
	○ Transaortic, 0 (0%) • Valve size: ○ 23 mm, 31 (26.3%) ○ 26 mm, 48 (40.7%) ○ 29 mm, 37 (31.4%) ○ 31 mm, 2 (1.7%) • Mean calcium score: 4092 (2177) HU **Population source:** consecutive patients matching inclusion criteria at single hospital in France between November 2013 and May 2014 (received a first generation TAVI valve). Note that a second group enrolled between September 2014 and October 2016 (received new generation TAVI valves) were also discussed, but no useable results were provided for this second group.
Prognostic variable	Calcium score >6,000 HU Calcium score ≤6,000 HU (referent) Pre-intervention electrocardiogram-gated noncontrast and contrast-enhanced multislice CT scan performed within 2 weeks prior to the procedure for valve and vascular access evaluation. Stored for post-processing and calcium scoring. Region of interest was selected from upper part of LV outflow tract to the leaflet tips. Calcifications were automatically detected by software with detection cutoff from 130 HU. Aortic valve calcification was then evaluated using Agatston software on transverse view. The threshold used, >6,000 HU, was identified using cutoff analysis and had the best predictive value, and was subsequently used in the multivariate analysis.
Confounders	Multivariate logistic regression analysis. Backward selection of variables with alpha-to-exit of 0.10. Factors included in adjusted analysis: not reported. Unclear which variables included in multivariate analysis, though possible that the 1 pre-specified confounder for this outcome (age) has been.
Outcomes and effect sizes	**All-cause mortality, stroke, myocardial infarction, heart failure or rehospitalisation for cardiac causes – 1 month following procedure** **OR 106.0 (95% CI 15.5 to 727.6, P<0.01) for >6,000 HU vs. ≤6,000 HU**

Reference	Akodad 2018[8]
	During the first month, the primary endpoint occurred in 28/118 patients (23.7%). This included 4 deaths during the index hospitalisation (n=3 due to annulus rupture and n=1 due to prosthesis migration). A further 4 patients died due to heart failure during the follow-up (n=3 presented with severe aortic regurgitation and n=1 presented with moderate aortic regurgitation). **Rehospitalisation – 1 month following procedure** **OR 23.24 (95% CI 2.39 to 100.07, P<0.0001) for >6,000 HU vs. ≤6,000 HU** Unclear whether this captured only rehospitalisation for cardiac causes or any rehospitalisation. Data on in-hospital outcomes were collected from medical records. One-month follow-up information was obtained using a phone questionnaire. Mean (range) follow-up: not reported. Events only followed up to 1 month following procedure.
Comments	**All-cause mortality, stroke, myocardial infarction, heart failure or rehospitalisation for cardiac causes – 1 month following procedure** Risk of bias: 1. Study participation HIGH 2. Study attrition LOW 3. Prognostic factor measurement HIGH 4. Outcome Measurement HIGH 5. Study confounding HIGH 6. Statistical analysis HIGH 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH Indirectness: • Population – unclear whether population represents target population of those where further tests are required to determine whether there is an indication for intervention, as all had TAVI. Not all had symptomatic severe AS as only ~50% with NYHA ≥3, but likely to have included some with symptomatic severe AS. • Prognostic factor – threshold of >6,000 HU used very different to that specified in protocol and was not different for men and women. Downgraded for this as part of risk of bias rating, so not downgraded further for indirectness.

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

Reference	Aksoy 2014[9]
Study type and analysis	Retrospective cohort study Cox proportional hazards analysis USA
Number of participants and characteristics	N=51 High aortic valve calcification on CT (>2027 Agatston units), n=26 Low aortic valve calcification on CT (≤2027 Agatston units), n=25 Low-flow low-gradient severe AS (severe based on valve area <1.0 cm^2) **Inclusion criteria:** Severe AS based on valve area <1.0 cm^2 on echocardiography; low-flow low gradient AS based on ejection fraction ≤25% and mean aortic valve gradient <25 mmHg on echocardiography; concurrent chest or cardiac CT performed without contrast. **Exclusion criteria:** Not reported. **Values listed below are presented as mean (SD) or number (%)** <u>Calcium score >2027 AU</u> • Age: 78.0 (8.3) years • Male/female: 15/11 (58%/42%) • Hypertension, 26 (100%) • Hyperlipidaemia, 23 (88%) • Diabetes mellitus, 15 (58%) • History of myocardial infarction, 21 (81%) • History of coronary artery bypass grafting, 18 (69%) • History of atrial fibrillation, 10 (38%) • History of stroke, 4 (15%) • History of chronic obstructive pulmonary disease, 9 (34%)

Reference	Aksoy 2014[9]
	• Baseline creatinine: 1.6 (0.7) • Ejection fraction: 21.1 (5.2)% • Aortic valve area: 0.7 (0.1) cm^2 • Peak aortic valve pressure gradient: 39.2 (9.2) mmHg • Mean aortic valve pressure gradient: 21.3 (4.4) mmHg • Aortic insufficiency ≥3, 1 (4%) • Mitral regurgitation ≥3, 6 (23%) • Right ventricular systolic pressure: 49.5 (13.2) mmHg Calcium score ≤2027 AU • Age: 71.0 (10.1) years • Male/female: 21/4 (84%/16%) • Hypertension, 21 (84%) • Hyperlipidaemia, 20 (80%) • Diabetes mellitus, 15 (60%) • History of myocardial infarction, 21 (84%) • History of coronary artery bypass grafting, 17 (68%) • History of atrial fibrillation, 12 (48%) • History of stroke, 6 (23%) • History of chronic obstructive pulmonary disease, 2 (8%) • Baseline creatinine: 1.6 (0.8) • Ejection fraction: 20.4 (4.9)% • Aortic valve area: 0.7 (0.1) cm^2 • Peak aortic valve pressure gradient: 31.7 (10.4) mmHg • Mean aortic valve pressure gradient: 16.6 (4.8) mmHg • Aortic insufficiency ≥3, 1 (4%) • Mitral regurgitation ≥3, 5 (20%) • Right ventricular systolic pressure: 46.3 (15.4) mmHg

Reference	Aksoy 2014[9]
	Population source: patients from single echocardiography database at Cleveland Clinic, retrospectively reviewed data between 1st January 2000 and 26th September 2009 for those matching inclusion criteria. Consecutive patients matching criteria.
Prognostic variable	High aortic valve calcification score on CT (>2027 Agatston units) Low aortic valve calcification score on CT (≤2027 Agatston units) (referent) Aortic valve calcification on CT measured using calcium-scoring software on clinical workstation. Threshold of 130 Hounsfield units used. Single user marked calcification of aortic valve leaflets in axial view. Calcification extending to LV outflow tract, coronary arteries and aorta were excluded if they were contiguous with the calcification on the valve and only the calcium on leaflets and annulus was included in the analysis. Agatston units were used to describe total calcium score. Calcium scoring of valve using CT led to median score of 2027 AU (range, 140-9210 AU), which was used to assign patients to high- and low-calcium score groups. Mean (SD) time between echocardiograms and CT scans without contrast was 110 (220) days.
Confounders	Adjusted survival analysis said to be performed using semiparametric Cox proportional hazard modelling. Factors adjusted for the analysis included those that did or did not have AVR: baseline comorbid conditions (list not provided) and echocardiographic parameters (ejection fraction, peak aortic valve gradient and mean aortic valve gradient). Note that no adjusted data was available for the separate AVR and no AVR groups.
Outcomes and effect sizes	**Mortality during follow-up – group that did not receive AVR during follow-up (non-operative mortality) – no adjustment** Report states that in those that did not receive AVR during follow-up, a high calcium score was associated with reduced survival compared to those with low calcium scores, as demonstrated by a Kaplan-Meier plot (P-value: 0.046). Follow-up on the graph is up to ~5 years in those that did not receive AVR. Insufficient data reported to be able to estimate HR. Unclear number of events in the low and high calcium groups that underwent AVR during follow-up. Note that although all of those in this group did not receive AVR, they may instead have received valvuloplasty, as n=5 in the high calcium group and n=1 in the low calcium group were reported to have had valvuloplasty during follow-up. Note that there was also one patient in the low calcium group that did not receive AVR but received total artificial heart placement and subsequent heart transplantation. **Mortality during follow-up – group that received AVR during follow-up (postoperative mortality) – no adjustment** 30 days post-surgical AVR **HR 1.00 (95% CI 0.10 to 9.64) for high calcium score vs. low calcium score**

Reference	Aksoy 2014[9]
	This is based on event rates of 2/11 in the low calcium group and 1/10 in the high calcium group, in those that received surgical AVR during follow-up, with a P-value of 1.0 reported in the paper. Note that although all patients in these two groups received AVR, the outcome does not represent postoperative mortality completely, as other patients received valvuloplasty or total artificial heart placement and heart transplantation, which could also be considered operative procedures. In addition, there was one additional participant in the high calcium group that received TAVI rather than surgical AVR that was not included in this analysis, as the study did not report whether they were alive within this 30-day time period. Long-term data An estimated HR for longer term follow-up could not be extracted due to insufficient data reported in the study, as the number of events in each group over a longer time-period was not reported. However, the report stated that the mortality of patients with high calcium scores was no different than that of those with low calcium scores during long-term follow-up, as demonstrated by a Kaplan-Meier plot (P-value: 0.39). Follow-up on the graph is up to ~9 years in those that received AVR. A total of 11 patients in the low calcium group and 10 patients in the high calcium group received surgical AVR during follow-up, with an additional patient in the high calcium group receiving TAVI. Note that although all patients in these two groups received AVR, the outcome does not represent postoperative mortality completely, as other patients received valvuloplasty or total artificial heart placement and heart transplantation, which could also be considered operative procedures. **Mortality during follow-up – mixture of those that did and did not receive AVR, included as factor in MV analysis** Report states that there was significantly better survival in patients with low calcium scores after adjustment for baseline comorbid conditions, ejection fraction, peak aortic valve gradient, mean aortic valve gradient and whether aortic valve replacement was performed during follow-up, as demonstrated by a Kaplan-Meier plot (P-value: 0.049). Follow-up on the graph is up to 5 years. Insufficient data reported to be able to estimate HR. Unclear number of events in the low calcium group as it was unclear whether the patient excluded for having a heart transplant did or did not experience the event, though event rate was 17/26 in the high calcium group and either 13/24 or 12/24 in the low calcium group. Though adjusted for aortic valve replacement during follow-up, other patients may have had valvuloplasty during follow-up that was not adjusted for in this analysis. Mortality assessed using Social Security Death Index and electronic medical records. A total of 30 patients died during follow-up. Of these deaths, 13 were in the low-calcium score group and 17 were in the high-calcium score group. During follow-up, 21 had surgical aortic valve replacement (11 in low-calcium group and 10 in high-calcium group) and 1 had TAVI (high-calcium group). In addition, 1 had total artificial heart placement followed by a heart transplant (low-calcium group – this patient

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

Reference	Clavel 2014[63]
Study type and analysis	Prospective cohort study Multivariate Cox proportional hazards model USA, France and Canada
Number of participants and characteristics	N=794 Severe aortic valve calcification (AVC) – ≥2,065 AU in men and ≥1,274 in women, n=410 Non-severe AVC – <2,065 AU in men and <1,274 AU in women, n=384

Reference	Clavel 2014[63]
	At least mild aortic stenosis (mean gradient ≥15.0 mmHg, peak aortic jet velocity ≥2.0 m/s or aortic valve area ≤2.0 cm^2) under conservative management. Appears to be a mixture of asymptomatic and symptomatic patients. Unclear whether there is any uncertainty about whether they should undergo intervention or not at time of study. **Inclusion criteria:** At least mild aortic stenosis (mean gradient ≥15.0 mmHg, peak aortic jet velocity ≥2.0 m/s or aortic valve area ≤2.0 cm^2); underwent comprehensive Doppler echocardiography and multidetector (MD) CT within same episode of care (<3 months between evaluations). **Exclusion criteria:** <18 years old; rheumatic valve disease or endocarditis; congenital heart disease (except bicuspid aortic valve); moderate or severe aortic regurgitation or mitral valve disease; history of valve repair or implantation. **Values listed below are presented as mean (SD) or number (%)** <u>Whole cohort – data not given separately for severe AVC and non-severe AVC</u> • Age: 73 (12) years • Male/female: 520/274 (65%/35%) • Body mass index: 28.3 (5.9) kg/m^2 • Body surface area: 1.90 (0.24) m^2 • Systolic blood pressure: 129 (19) mmHg • Diastolic blood pressure: 71 (11) mmHg • Heart rate: 68 (13) bpm • Heart failure symptoms, 211 (27%) • Hypertension, 544 (69%) • Coronary artery disease, 347 (44%) • Diabetes, 180 (23%) • Hyperlipidaemia, 534 (67%) • Previous coronary artery bypass grafting, 183 (23%) • Peak aortic jet velocity: 3.7 (1.0) m/s • Mean aortic gradient: 35 (19) mmHg

Reference	Clavel 2014[63]

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

Prognostic variable	Severe AVC – ≥2,065 AU in men and ≥1,274 in women Non-severe AVC – <2,065 AU in men and <1,274 AU in women (referent) Non-contrast CT was performed using MDCT scanners. The same methods for image acquisition and interpretation were used across the three centres. Validated software used to measure aortic valve calcification (AVC) by Agatston method and expressed in arbitrary units (AU). Threshold used had previously been demonstrated to be the best cutoff for severe AVC and was therefore used in the study. Technologists and cardiologists performing CT were blinded to clinical, Doppler echocardiographic and outcome data. Median time between Doppler echocardiography and MDCT was 1 day (IQR: 0-9 days).
Confounders	Multivariate Cox proportional hazards model. Clinically relevant variables and/or variables with a P-value of ≤0.05 on univariate analysis were included in multivariate models. Multiple models extracted as all accounted for same number of variables. Factors included in adjusted analysis: • Model 1: age, sex, NYHA class ≥III, diabetes, history of coronary artery disease, indexed aortic valve area, mean gradient and left ventricular ejection fraction

Reference	Clavel 2014[63]
	• Model 2: age, sex, NYHA class ≥III, diabetes, history of coronary artery disease, absolute aortic valve area, mean gradient and left ventricular ejection fraction (indexed aortic valve area in model 1 replaced with absolute aortic valve area) • Model 3: age, sex, NYHA class ≥III, diabetes, history of coronary artery disease, absolute aortic valve area, peak aortic jet velocity (Vmax) and left ventricular ejection fraction (mean gradient in model 1 replaced with Vmax) The above factors include age which is listed in the protocol as a confounder for non-operative mortality, though the other factor listed, smoking, is not included.
Outcomes and effect sizes	**Mortality under medical treatment – up to 5 years** • **HR 1.75 (95% CI 1.04 to 2.92, P=0.03) for severe AVC vs. non-severe AVC – model 1** • **HR 1.71 (95% CI 1.05 to 2.84, P=0.03) for severe AVC vs. non-severe AVC – model 2** • **HR 1.71 (95% CI 1.02 to 2.90), P=0.04) for severe AVC vs. non-severe AVC – model 3** When aortic valve implantation occurred, follow-up was considered to have ended for this analysis. This included transcatheter or surgical aortic valve implantation. During follow-up under medical management, 115 deaths occurred (n=82 were cardiovascular-related). Overall 5-year survival post-diagnosis was 65±3% under medical management. Mean (SD) follow-up under medical management: 1.7 (2.0) years. Follow-up up to death, aortic valve implantation or ≥5 years post-diagnosis was completed in 762 patients (96%).
Comments	**Mortality under medical treatment – up to 5 years (applicable for all 3 models reported)** Risk of bias: 1. Study participation LOW 2. Study attrition HIGH 3. Prognostic factor measurement LOW 4. Outcome Measurement LOW 5. Study confounding HIGH 6. Statistical analysis LOW 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH Indirectness: • Population – unclear whether this represents a population where there is uncertainty about whether or not intervention should be performed, or whether all underwent CT as part of the prospective study, regardless of likely treatment.

Reference	Clavel 2014[63]
	• Confounding factors – though adjustment for one of the confounders pre-specified in the protocol has been performed (age) as well as other factors, the other pre-specified confounder for this outcome (smoking) was not included. Downgraded for this as part of risk of bias rating, so not downgraded further for indirectness.

Reference	Fischer-Rasokat 2020[94]
Study type and analysis	Retrospective cohort study Multivariate Cox proportional hazards model Germany
Number of participants and characteristics	N=650 High aortic valve calcification (AVC): ≥2,000 AU in men and ≥1,200 in women, n=428 Non-severe AVC – <2,000 AU in men and <1,200 AU in women, n=222 Analysis of data from a TAVI registry, referred based on local heart team decision. Appears to be a mixture of asymptomatic and symptomatic patients. Unclear whether there is any uncertainty about whether they should undergo intervention or not at time of study. **Inclusion criteria:** Severe aortic stenosis (AVAi <0.6cm/m^2) treated by the transfemoral approach with data from at last the 30-day follow-up. **Exclusion criteria:** Bicuspid aortic valve, no information on SVi or AVC. High-gradient aortic stenosis (mean pressure gradient ≥40 mmHg). *This group served as controls in the study but are not include in the analysis relevant to this review.* **Values listed below are presented as mean (SD), median (IQR) or number (%)** **Low AVC (n=222)** **High AVC (n=428)** Age (years) 81 (78-85) 82 (79-85) Female 46.8% 51.4% NYHA class III/IV 86.0% 82.9%

Reference	Fischer-Rasokat 2020[94]		
	CAD	66.2%	64.0%
	Prior MI	17.6%	15.2%
	Atrial fibrillation	56.8%	53.5%
	LVEF	60 (45-65)%	60 (45-65)%
	AVC in women (AU)	887 (680-1016)	1848 (1487-2387)
	AVC in men (AU)	1542 (1251-1789)	2903 (2411-3627)
	Population source: patients recruited one high-volume centre. Time period not stated.		
Prognostic variable	High AVC: ≥2,000 AU in men and ≥1,200 in women Low AVC: <2,000 AU in men and <1,200 AU in women (referent) Non-contrast CT was performed using MDCT scanners. Validated software used to measure aortic valve calcification (AVC) by Agatston method and expressed in arbitrary units (AU). Threshold used had previously been reported.		
Confounders	Multivariate Cox proportional hazards model. Baseline parameters with a P-value of <0.1 on univariate analysis were included in multivariate models. Factors included in adjusted analysis: BMI, GFR, dyslipidaemia, LV hypertrophy, mean pressure gradient, aortic valve area index, balloon expandable valve, rapid pacing, residual AR. The above factors do not include age or smoking.		
Outcomes and effect sizes	**All-cause mortality after TAVI – 1 year** • **HR 1.320 (95% CI 0.771, 2.258) for high AVC vs. low AVC** Patients still in follow-up after 1 year were censored as alive. During 1 year follow-up, 92 deaths occurred (31 in low and 61 in high AVC groups).		
Comments	**Mortality 1 year after TAVI** Risk of bias: 1. Study participation LOW 2. Study attrition LOW 3. Prognostic factor measurement LOW		

Reference	Fischer-Rasokat 2020[94]	
	4. Outcome Measurement	HIGH
	5. Study confounding	HIGH
	6. Statistical analysis	HIGH
	7. Other risk of bias	LOW
	OVERALL RISK OF BIAS	VERY HIGH
	Indirectness: • Population – all already scheduled for aortic valve intervention so no uncertainty about whether there is indication for intervention. • Confounding factors –the pre-specified confounder for this outcome (age) was not included. Downgraded for this as part of risk of bias rating, so not downgraded further for indirectness.	

Reference	Larsen 2016[152]
Study type and analysis	Prospective cohort study Multivariable Cox proportional hazards regression model, **but only univariate for our variable of interest**
Number of participants and characteristics	**Total n=116** (note 1 patient not evaluated for calcium density on CT) Severe AV calcium density on MDCT (>300 AU/cm^2 for women and >475 AU/cm^2 for men), n=45 No severe AV calcium density n = 70 **Inclusion criteria** Asymptomatic aortic stenosis. Asymptomatic defined by the treating physician, with a peak velocity by continuous wave Doppler >2.5 m/s **Exclusion criteria** P-creatinine >130 mmol/l, allergy to contrast, LVEF <50% on echo or known malignant disease **Values listed below are presented as mean (SD), median (IQR) or number (%)**

Reference	Larsen 2016[152]
	Patient characteristics: Age: 72 (8) years Male: 73% Mean AVA by TTE: 1.01 (0.30) cm^2 Current smoker: 16% Past smoker: 57% Systolic blood pressure, mmHg: 145 (20) **Population source**: six hospitals in the Greater Copenhagen area Consecutive sample, September 2009 – January 2012
Prognostic variable	Severe AVC density on MDCT All patients had a thorough clinical work-up, including an electrocardiogram, lung function test, 6-minute walk test, and blood samples including pro-BNP. By September 2013 information on mortality and indication of AVR was obtained from the electronic health record by a systematic review of hospital contacts (outpatient visits and acute admissions) after the baseline examination. The reviewer was blinded to all echocardiographic data. The treating physician was blinded to the results of the echocardiographic examination and the MDCT performed in the present study and referral for AVR was performed independently by the clinical heart team. AVC was indexed by aorta annulus area (AVC density) and severe AVC density was defined as >300 AU/cm^2 for women and >475 AU/cm^2 for men. AVC by Agatston was defined as calcification of the aortic leaflets, including the attachment points of the leaflets. Calcification of the aortic wall immediately connected to the calcification of the aortic valve was also included. Careful consideration was provided to avoid including calcification from ostium of coronary arteries, the mitral annulus and the mitral valve.
Confounders	Univariate Cox regression model only for factors in our protocol
Outcomes and effect sizes	**47 patients reached the endpoint of indication for AVR** and no patients experienced sudden cardiac death. The indication for AVR was reduced LVEF without symptoms in one patient and symptoms in the rest. **Unadjusted hazard ratios for indication for AVR** 1.0 (1.00-1.00) for severe AVC vs non-severe

Reference	Larsen 2016[152]
	Number with events in prognostic groups not reported and unable to read off reliable estimate from KM curves, as values do not match reported event rate Median follow-up of 27 (IQR 19–44) months
Comments	Risk of bias: 1. Study participation HIGH 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement HIGH 5. Study confounding HIGH 6. Statistical analysis HIGH 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH Indirectness: • Indirect prognostic factor definitions • Confounding - only unadjusted effect estimate available, with no adjustment for any variables, including those specified in protocol. Downgraded for this as part of risk of bias rating, so not downgraded further for indirectness.

Reference	Ludwig 2020[162]
Study type and analysis	Retrospective cohort study Multivariate Cox proportional hazards model Germany
Number of participants and characteristics	N=526 **Low-flow, low-gradient group (n=290)** Low AVC density (1st tertile, median 361.5 [239.2-447.0] mm^3 calcium/cm^2): n=96 Moderate AVC density (2nd tertile; median 772.8 [635.9-907.7] mm^3 calcium/cm^2): n=96

Reference	Ludwig 2020[162]

High AVC density (3rd tertile; median 1672.9 [1354.9-2167.6] mm^3 calcium/cm^2): n=98

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

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

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

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

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

	Low AVC (n=222)	**High AVC (n=428)**
Age (years)	81 (78-85)	82 (79-85)
Female	46.8%	51.4%
NYHA class III/IV	86.0%	82.9%
CAD	66.2%	64.0%
Prior MI	17.6%	15.2%
Atrial fibrillation	56.8%	53.5%
LVEF	60 (45-65)%	60 (45-65)%
AVC in women (AU)	887 (680-1016)	1848 (1487-2387)
AVC in men (AU)	1542 (1251-1789)	2903 (2411-3627)

Reference	Ludwig 2020[162]
	Population source: patients recruited at one high-volume centre from 2008-2018.
Prognostic variable	Aortic valve calcium density on CT (based on total calcium in the annular plane and the LVOT: high, medium, low (referent) Non-contrast CT was performed using MDCT scanners. Aortic valve calcification (AVC) was the composite total calcium score from the annular plane and the LVOT. The density was the ratio of AVC per aortic annulus area (cm^2).
Confounders	Multivariate Cox proportional hazards model. Baseline parameters with a P-value of <0.25 on univariate analysis were used in a forward selection process in multivariate models. Factors included in adjusted analysis: Age, BMI, diabetes, COPD, atrial fibrillation, prior myocardial infarction (for pLFLG only), and non-TF access. The above factors do not include smoking.
Outcomes and effect sizes	**All-cause mortality after TAVI – 3 years** • **HR for high vs moderate or low AVC density in LEF LG: 0.73 (0.60, 0.88)** • **HR for high vs moderate or low AVC density in pLFLG: 0.91 (0.73, 1.14).** **Better outcome in high calcium density group** During 1 year follow-up, 100 deaths occurred in LEF LG group (24, 38 and 38 in high, moderate and low AVC density groups, respectively) and 54 deaths occurred in PLF LG group (18, 16 and 20 in high, moderate and low AVC density groups, respectively).
Comments	**Mortality 1 year after TAVI** Risk of bias: 1. Study participation LOW 2. Study attrition LOW 3. Prognostic factor measurement HIGH 4. Outcome Measurement LOW 5. Study confounding LOW 6. Statistical analysis LOW 7. Other risk of bias LOW OVERALL RISK OF BIAS HIGH

Reference	Ludwig 2020[162]
	Indirectness: • Population – all already scheduled for aortic valve intervention so no uncertainty about whether there is indication for intervention.

Reference	Pawade 2018[212]
Study type and analysis	Multicentre registry – appears to be mainly prospective data, though may have some retrospective elements for certain patients Data from multiple prospective cohort studies (5 studies from 3 centres) provided and also data of those being considered for TAVI and that were undergoing CT scans as part of their work up (from 5 centres). All pooled into registry used for this study. Cox proportional hazards regression UK (Scotland – 1 centre, England – 1 centre), France (3 centres), Canada (1 centre), Spain (1 centre), USA (1 centre)
Number of participants and characteristics	N=918 overall (n=431 in prospective clinical research studies and n=487 imaged as part of routine clinical care) • N=215 with outcome data in whole cohort Includes various presentations of aortic stenosis (AS), including mild-severe. Symptom status appears to vary between patients – includes some severe symptomatic and also non-severe symptomatic, as well as some where the different echocardiography measures of AS severity are not in agreement (discordant group). Overall, population likely represents target population of review as states that those where a decision to perform an intervention had already been made at the time of CT were excluded from the outcome analysis, suggesting the remaining patients included in outcome analysis were those where there was uncertainty about whether or not to refer for intervention. Severe aortic valve calcification (AVC) on CT (≥1377 AU for women and ≥2062 AU for men), n= not reported Non-severe AVC on CT (<1377 AU for women and <2062 AU for men), n= not reported Severe AVC on CT (≥1274 AU for women and ≥2065 AU for men) – previously published threshold used, n= not reported Non-severe AVC on CT (<1274 AU for women and <2065 AU for men), n= not reported **Inclusion criteria:** At least mild AS (peak aortic jet velocity >2.5 m/s or mean gradient >10 mmHg); undergone electrocardiogram-gated CT calcium scoring within 3 months of echocardiogram.

Reference	Pawade 2018[212]
	Exclusion criteria: Established rheumatic heart disease; other forms of valvular heart disease of at least moderate severity; estimated glomerular filtration rate <30 ml/min per 1.73 m^2. **Values listed below are presented as mean (SD) or number (%)** <u>Whole cohort (n=918 – data not provided separately for those with outcome data)</u> • Age: 77 (10) years • Male/female: 551/367 (60%/40%) • Body surface area: 1.88 (0.25) m^2 • Body mass index: 28 (6) kg/m^2 • Systolic blood pressure: 136 (20) mmHg • Diastolic blood pressure: 72 (12) mmHg • Heart rate: 69 (13) bpm • Possible symptoms, 643 (70%) • Hypertension, 707 (77%) • Coronary artery disease, 413 (45%) • Ever smoked, 294 (32%) • Diabetes mellitus, 257 (28%) • Hyperlipidaemia, 597 (65%) • Scan interval, median (IQR): 5 (1-25) • Peak aortic jet velocity: 3.88 (0.90) mmHg • Peak aortic jet velocity ≥4 m/s, 468 (51%) • Mean gradient: 38 (19) mmHg • Mean gradient ≥40 mmHg, 441 (48%) • Aortic valve area: 0.90 (0.35) cm^2 • Aortic valve area ≤1.0 cm^2, 615 (67%) • Aortic valve area index: 0.48 (0.18) cm^2/m^2

Reference	Pawade 2018[212]
	• Aortic valve area index ≤0.6 cm^2, 707 (77%) • Bicuspid, 64 (7%) • LV outflow tract diameter: 2.14 (0.22) cm • LV outflow tract area: 3.60 (0.76) cm^2 • Indexed stroke volume: 42 (11) ml/m^2 • Valsalva diameter: 3.32 (0.46) cm • Tubular diameter: 3.05 (0.57) cm • Ejection fraction: 61 (8.5)% • AVC score, median (IQR): 2055 (1054-3339) AU • AVC index, median (IQR): 1088 (557-1810) AU/m^2 • AVC density, median (IQR): 580 (284-940) AU/cm^2 • AVC volume, median (IQR): 1158 (594-2189) mm^3 **Population source:** data was provided by 8 different international centres. Of these, 3 (Edinburgh, Paris and Québec) provided data from 5 prospective AS clinical research studies and 5 (Europe and USA) provided data of those being considered for TAVI and that were undergoing CT scans as part of their work up, which formed a multicentre registry used in this study. Unclear whether consecutive. Though 2 of the centres had already reported threshold results for CT AVC, data provided for this study were from distinct populations of patients that did not overlap with their original cohorts.
Prognostic variable	Severe AVC on CT (≥1377 AU for women and ≥2062 AU for men) Non-severe AVC on CT (<1377 AU for women and <2062 AU for men) (referent) Severe AVC on CT (≥1274 AU for women and ≥2065 AU for men) – previously published threshold used Non-severe AVC on CT (<1274 AU for women and <2065 AU for men) (referent) All centres performed noncontrast CT scans from 75%-80% of R-R interval. Imaging performed on different scanners depending on centre. Some centres used beta-blockade to achieve target resting heart rate of ≤65 bpm. Imaging analysis performed at each centre using range of different software packages. Method for calcium scoring was agreed at start of study and was applied at all centres. CT-AVC scores quantified on 3 mm axial slices starting at base of the valve. Calcium originating from extravalvular structures such as

Reference	Pawade 2018[212]
	mitral valve annulus, ascending aorta and coronary arteries was excluded. Total AVC in AU was calculated and indexed to body surface area (AU/m^2) or divided by LV outflow tract area on echocardiography to estimate calcium density (AU/cm^2). Optimal thresholds of CT-AVC for identifying severe AS in this study were 1377 AU for women and 2062 AU for men. These were subsequently used to assess the effect of CT-AVC on prognosis. In addition, thresholds used from a previously published study (1274 AU for women and 2065 AU for men) were also used to assess prognosis in this study.
Confounders	Multivariate Cox proportional hazards regression Factors included in adjusted analysis: • Severe AVC on CT (≥1377 AU for women and ≥2062 AU for men) vs. non-severe AVC on CT (<1377 AU for women and <2062 AU for men): age, sex, Vmax ≥4 m/s and aortic valve area <1 cm^2 • Severe AVC on CT (≥1274 AU for women and ≥2065 AU for men) vs. non-severe AVC on CT (<1274 AU for women and <2065 AU for men): age, sex, Vmax ≥4 m/s and aortic valve area <1 cm^2 One of the pre-specified confounders (age) was included in the multivariate analysis for both thresholds. However, the other (smoking) was not included, though a number of other factors were included.
Outcomes and effect sizes	**Death or aortic valve replacement (AVR) during follow-up – whole cohort, n=219 – adjusted for age, sex, Vmax ≥4 m/s and aortic valve area <1 cm^2** **HR 3.90 (95% CI 2.19 to 6.78, P<0.001) for severe AVC on CT (≥1377 AU for women and ≥2062 AU for men) vs. non-severe AVC on CT (<1377 AU for women and <2062 AU for men)** **HR 3.80 (95% CI 2.16 to 6.69, P<0.001) for severe AVC on CT (≥1274 AU for women and ≥2065 AU for men) vs. non-severe AVC on CT (<1274 AU for women and <2065 AU for men)** A total of 79 patients experienced events in the whole cohort (n=59 underwent AVR and n=20 deaths). AVR included surgical procedures and transcatheter AVR. Decisions about whether to proceed to AVR were made according to international clinical guidelines, independent of CT-AVC and after multidisciplinary discussion – this definition suggests that AVR events captured were not planned just prior to CT, though may have been planned following CT rather than being an emergency intervention. Patients in whom a decision to refer for AVR had already been made at the time of CT-AVC or who had CT imaging performed as part of the work up before transcatheter AVR or surgery were excluded from the outcome analysis. Median (IQR) follow-up for whole cohort: 1029 (126-2251) days.

Reference	Pawade 2018[212]
Comments	**Death or AVR during follow-up – whole cohort, n=219 – thresholds of 1377 AU for women and 2062 AU for men** Risk of bias: 1. Study participation HIGH 2. Study attrition HIGH 3. Prognostic factor measurement LOW 4. Outcome Measurement HIGH 5. Study confounding HIGH 6. Statistical analysis LOW 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH Indirectness: • Outcome – composite outcome of two separate outcomes listed in the protocol, rather than reporting them separately. Unclear whether AVR outcome represents unplanned intervention as specified in our protocol, as some may have been emergency operations while others may have been planned following results of CT scan and discussion with team. • Confounding – though adjustment for one of the confounders pre-specified in the protocol has been performed (age) as well as other factors, the other pre-specified confounder for this outcome (smoking) was not included. Downgraded for this as part of risk of bias rating, so not downgraded further for indirectness. **Death or AVR during follow-up – whole cohort, n=219 – thresholds of 1274 AU for women and 2065 AU for men** Risk of bias: 1. Study participation HIGH 2. Study attrition HIGH 3. Prognostic factor measurement LOW 4. Outcome Measurement HIGH 5. Study confounding HIGH 6. Statistical analysis LOW 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH Indirectness:

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

Reference	Utsunomiya 2013[275]
Study type and analysis	Prospective cohort study Cox regression analysis Japan
Number of participants and characteristics	N=64 <u>Whole cohort (asymptomatic mild-severe AS) analyses (n=64)</u> Aortic valve calcium (AVC) score (AVCS) ≥723, n=32 AVCS <723, n=32 <u>Asymptomatic severe AS subgroup analyses (n=29)</u> AVCS ≥1266, n=14 AVCS <1266, n=15 Asymptomatic AS. Mild or moderate in 55% and severe in 45%. **Inclusion criteria:** Asymptomatic calcific aortic stenosis (AS; peak transaortic velocity >2.5 m/s by Doppler ultrasound, calcification of aortic valve); left ventricular ejection fraction >50% on echocardiography; stable for 6 months prior to enrolment; provided informed consent for inclusion in the study.

Reference	Utsunomiya 2013[275]
	Exclusion criteria: Symptoms thought to be related to AS; aortic regurgitation of at least moderate severity; previous or scheduled aortic valve replacement; bicuspid aortic valve; irregular heart rhythm (e.g. atrial fibrillation); prior myocardial infarction or coronary revascularisation; serum creatinine >0.13 mmol/L. **Values listed below are presented as mean (SD) or number (%)** <u>Overall cohort</u> • Age: 74 (7) years • Male/female: 28/36 (44%/56%) • Systolic blood pressure: 137 (19) mmHg • Diastolic blood pressure: 74 (12) mmHg • Heart rate: 70 (10) bpm • Peak transaortic velocity: 3.75 (1.07) m/s • Peak transaortic velocity ≥4 m/s, 22 (34%) • Mean transaortic pressure gradient: 29 (18) mmHg • Aortic valve area: 1.14 (0.45) cm^2 • Left atrial volume index: 39 (12) ml/m^2 • Septal E/e': 15.2 (6.5) • Lateral E/e': 11.8 (5.3) • CCTA-derived aortic valve area: 1.36 (0.48) cm^2 • CCTA-derived LV ejection fraction: 69 (9)% • CCTA-derived LV mass index: 108 (32) g/m^2 • Multivessel obstructive CAD, 11 (17%) • AVCS, median (IQR): 723 (356-1284) <u>AVCS ≥723</u> • Age: 75 (7) years • Male/female: 18/14 (56%/44%)

Reference	Utsunomiya 2013[275]
	• Systolic blood pressure: 141 (21) mmHg • Diastolic blood pressure: 76 (14) mmHg • Heart rate: 71 (9) bpm • Peak transaortic velocity: 4.24 (0.86) m/s • Peak transaortic velocity ≥4 m/s, 20 (63%) • Mean transaortic pressure gradient: 39 (17) mmHg • Aortic valve area: 0.83 (0.27) cm^2 • Left atrial volume index: 43 (12) ml/m^2 • Septal E/e': 16.1 (6.4) • Lateral E/e': 13.3 (6.2) • CCTA-derived aortic valve area: 1.04 (0.32) cm^2 • CCTA-derived LV ejection fraction: 67 (9)% • CCTA-derived LV mass index: 123 (35) g/m^2 • Multivessel obstructive CAD, 7 (22%) • AVCS, median (IQR): 1266 (902-1569) <u>AVCS <723</u> • Age: 73 (7) years • Male/female: 10/22 (31%/69%) • Systolic blood pressure: 133 (17) mmHg • Diastolic blood pressure: 72 (11) mmHg • Heart rate: 70 (10) bpm • Peak transaortic velocity: 3.07 (0.48) m/s • Peak transaortic velocity ≥4 m/s, 2 (6%) • Mean transaortic pressure gradient: 18 (11) mmHg • Aortic valve area: 1.45 (0.37) cm^2

Reference	Utsunomiya 2013[275]
	• Left atrial volume index: 35 (11) ml/m^2 • Septal E/e': 14.2 (6.6) • Lateral E/e': 10.3 (3.8) • CCTA-derived aortic valve area: 1.68 (0.39) cm^2 • CCTA-derived LV ejection fraction: 71 (9)% • CCTA-derived LV mass index: 93 (19) g/m^2 • Multivessel obstructive CAD, 4 (13%) • AVCS, median (IQR): 361 (265-574) **Population source:** appear to have been enrolled from a single institute. Time period unclear. Unclear if consecutive patients.
Prognostic variable	Whole cohort (asymptomatic mild-severe AS) analyses (n=64) AVCS ≥723 AVCS <723 (referent) Asymptomatic severe AS subgroup analyses (n=29) AVCS ≥1266 AVCS <1266 (referent) Cardiac CT angiography (CCTA) examinations were performed using multidetector-row CT scanner. Patients with heart rate ≥60 bpm were given an oral beta-blocker to achieve heart rate of 50-60 bpm. Sublingual nitroglycerin administered just before scanning. Dataset of contrast-enhanced scan reconstructed every 5% of R-R interval and transferred to a remote computer workstation. CCTA images were analysed by two experienced observers blinded to clinical and echocardiographic information. Reconstructed images through aortic valve and left ventricle were obtained using 25 cm field of view at 5% intervals throughout the cardiac cycle. AVC AVC qualitatively assessed using non-contrast axial images. AVCS was calculated using Agatston method and coronary calcium score. AVC was defined as calcification of the aortic valve leaflets just inferior to the origins of the coronary arteries, including the attachment points of the leaflets. Calcification of the aortic wall immediately connected to calcification of aortic valve leaflets was included in AVC. Threshold used for AVCS was based on the median value in the study, which was 723 for the whole cohort and 1266 for the asymptomatic severe subgroup.

Reference	Utsunomiya 2013[275]
	CCTA examinations were performed within 1 week of echocardiography.
Confounders	Cox regression analysis performed, with multivariate results not available for AVCS thresholds. For AVCS thresholds, estimates of a univariate HR were calculated using information provided in the Kaplan-Meier plots. Factors included in adjusted analysis: <u>Whole cohort (asymptomatic mild-severe AS):</u> • AVCS ≥723 vs. AVCS <723: unadjusted as calculated from information reported in the paper. <u>Asymptomatic severe AS subgroup:</u> • AVCS ≥1266 vs. AVCS <1266: unadjusted as calculated from information reported in the paper. For AVCS threshold prognostic factors, no adjustment for any of the factors listed in the protocol was performed.
Outcomes and effect sizes	**<u>Cardiac events – cardiac death, aortic valve replacement (AVR), non-fatal myocardial infarction and heart failure requiring urgent hospitalisation</u>** • **HR 6.08 (95% CI 2.86 to 12.92) for AVCS ≥723 vs. AVCS <723 – whole cohort (asymptomatic mild-severe AS, n=64)** • **HR 1.71 (95% CI 0.71 to 4.15) for AVCS ≥1266 vs. AVCS <1266 – asymptomatic severe AS subgroup (n=29)** **<u>Non-AVR cardiac events – cardiac death, non-fatal myocardial infarction and heart failure requiring urgent hospitalisation</u>** • **HR 3.69 (95% CI 1.39 to 9.84) for AVCS ≥723 vs. AVCS <723 – whole cohort (asymptomatic mild-severe AS, n=64)** • **HR 3.08 (95% CI 0.85 to 11.23) for AVCS ≥1266 vs. AVCS <1266 – asymptomatic severe AS subgroup (n=29)** During follow-up, 27 patients experienced events (n=5 cardiac deaths, n=11 AVR, n=3 non-fatal myocardial infarctions and n=8 heart failure requiring urgent hospitalisation). Coronary revascularisation performed in n=2 patients with multi-vessel obstructive CAD. Of the cardiac deaths, n=2 were due to out of hospital cardiac arrests in patients with severe AS and refusal of care, n=1 was due to proceeding angina pectoris with development of fatal myocardial infarction and n=2 were due to pump failure likely due to low output syndrome with subacute increase in shortness of breath one exertion. All patients that underwent AVR had severe AS at enrolment and reasons for AVR were rapid progression of AS with symptom deterioration (n=9) and critical AS (peak transaortic velocity >5.5 m/s) without symptoms (n=2). 2-year cardiac event-free survival was 64.6% and 2-year non-AVR cardiac event-free survival rate was 88.0%.

Reference	Utsunomiya 2013[275]
	AVCS 2-year cardiac event-free survival was 10.8% in those with AVCS ≥723 and 85.8% in those with AVCS <723. 2-year non-AVR cardiac event-free survival was also lower in AVCS ≥723 group compared with AVCS <723 group. In separate analyses for asymptomatic severe and asymptomatic mild-moderate AS, event-free survival was lower in patients with AVCS above median compared with those below the median value, for both cardiac events overall and non-AVR cardiac events. Patients were assessed every 6 months during follow-up. Event information was obtained from telephone interviews, contact with patient physicians and hospital records. Coronary revascularisation was not included in cardiac events. Myocardial infarction was defined as typical symptoms, new pathological Q waves on electrocardiogram or elevated serum creatine kinase level. Median (IQR) follow-up for whole cohort: 29 (18-50) months. Not reported separately for asymptomatic severe subgroup.
Comments	**Cardiac events – cardiac death, aortic valve replacement (AVR), non-fatal myocardial infarction and heart failure requiring urgent hospitalisation** AVCS ≥723 vs. AVCS <723 – whole cohort (asymptomatic mild-severe AS, n=64) Risk of bias: 1. Study participation — LOW 2. Study attrition — HIGH 3. Prognostic factor measurement — HIGH 4. Outcome Measurement — HIGH 5. Study confounding — VERY HIGH 6. Statistical analysis — HIGH 7. Other risk of bias — LOW OVERALL RISK OF BIAS — VERY HIGH Indirectness: • Population – unclear whether all represent a population where it was uncertain whether intervention is required, as includes a mixture of mild-severe asymptomatic AS, with only 45% being asymptomatic severe. • Prognostic factor – threshold based on median value and is the same for men and women, whereas ideally a separate threshold would be used for men and women, and the threshold is quite different to that specified in the protocol. Downgraded for this as part of risk of bias rating, so not downgraded further for indirectness.

Reference	Utsunomiya 2013[275]

- Confounding – results for this prognostic factor are unadjusted as no multivariate results using this threshold were reported. Pre-specified factors in the protocol have therefore not been taken into account. Downgraded for this as part of risk of bias rating, so not downgraded further for indirectness.
- Outcome – composite outcome consisting of multiple outcomes specified in the protocol, rather than reporting separately.

AVCS ≥1266 vs. AVCS <1266 – asymptomatic severe AS subgroup (n=29)

Risk of bias:

1. Study participation	LOW
2. Study attrition	HIGH
3. Prognostic factor measurement	HIGH
4. Outcome Measurement	HIGH
5. Study confounding	VERY HIGH
6. Statistical analysis	HIGH
7. Other risk of bias	LOW
OVERALL RISK OF BIAS	VERY HIGH

Indirectness:

- Prognostic factor – threshold based on median value and is the same for men and women, whereas ideally a separate threshold would be used for men and women, and the threshold is quite different to that specified in the protocol. Downgraded for this as part of risk of bias rating, so not downgraded further for indirectness.
- Confounding – results for this prognostic factor are unadjusted as no multivariate results using this threshold were reported. Pre-specified factors in the protocol have therefore not been taken into account. Downgraded for this as part of risk of bias rating, so not downgraded further for indirectness.
- Outcome – composite outcome consisting of multiple outcomes specified in the protocol, rather than reporting separately.

Non-AVR cardiac events – cardiac death, non-fatal myocardial infarction and heart failure requiring urgent hospitalisation

AVCS ≥723 vs. AVCS <723 – whole cohort (asymptomatic mild-severe AS, n=64)

Risk of bias:

1. Study participation	LOW
2. Study attrition	HIGH

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

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

Reference	Yoon 2020[291]
Study type and analysis	Retrospective and prospective cohort study (retrospective for cases performed before participation in the registry) Multivariate Cox proportional hazards model Denmark, France, Germany, Israel, Italy, the Netherlands, Switzerland, and USA
Number of participants and characteristics	N=1034 Numbers in risk groups not stated. **Inclusion criteria:** Bicuspid aortic valve undergoing TAVI for symptomatic severe AS **Exclusion criteria:** Suboptimal CT images, non-bicuspid aortic valve **Values listed below are presented as mean (SD), median (IQR) or number (%)** Age (years) 74.7 (9.3) Male 59.0% NYHA class III/IV 71.2% Prior MI 11.5% Prior atrial fibrillation 18.1%

Reference	Yoon 2020[291]
	LVEF 53.5 (15.3)% Transfemoral access 94.3% **Population source:** consecutive patients recruited from 24 cardiovascular centres across 8 countries. Time period not stated. Median follow-up 360 (100-575) days.
Prognostic variable	Excess leaflet calcification on CT: more than the median value for the cohort, >382 mm^3; ≤382 mm^3 (referent). Numbers in each group not stated. Intra- and inter-observer agreement for leaflet calcification had ICC of 0.999 and 0.999
Confounders	Multivariate Cox proportional hazards model. Baseline parameters with a P-value of <0.1 on univariate analysis were included in multivariate models. Factors included in adjusted analysis: Age, STS score, peripheral vascular disease, prior AF, calcified raphe, aortopathy, non-TF access.
Outcomes and effect sizes	**All-cause mortality after TAVI – 2 years** • **HR for high vs low AVC density: 2.33 (1.41, 3.85)** **Cardiovascular mortality after TAVI – 2 years** • **HR for high vs low AVC density: 2.83 (1.38, 5.81)** During 1 year follow-up, 86 deaths occurred. 2-year all-cause mortality was 18.9% in those with excess leaflet calcification and 6.5% in those with mild calcification.
Comments	**All-cause mortality 2 years after TAVI** Risk of bias: 1. Study participation HIGH 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement LOW 5. Study confounding LOW 6. Statistical analysis LOW 7. Other risk of bias LOW

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