D.3 Aortic stenosis – coronary artery disease on CT

Reference	Carstensen 2016[40]
Study type and analysis	Prospective cohort study Multivariable Cox regression model, **but no analysis for our variable of interest**
Number of participants and characteristics	**Total n=104** Normal coronary angiogram 18% (19) Atheromatosis 51% (53) One vessel 16% (17) Two vessel 12% (12) Three vessel 3% (3) **Inclusion criteria** Asymptomatic moderate–severe aortic stenosis (aortic valve area ,1.5 cm^2) with a peak velocity by continuous wave Doppler >2.5 m/s, defined by the treating physician, preserved LVEF ≥ 50%. No indication for AVR at baseline **Exclusion criteria** Atrial fibrillation or other severe heart valve disease **Values listed below are presented as mean (SD), median (IQR) or number (%)** **Patient characteristics:** Age: 72 (9) years Male: 68% AVA: 0.90 (0.75-1.14) cm^2

Reference	Carstensen 2016[40]		
	Current smoker: 17% EuroScore: 5.6 (2) Systolic blood pressure, mmHg: 145 (20) Chronic lung disease: 7% proBNP, pmol/L: 24 (13-51) **Population source**: six hospitals in the Greater Copenhagen area Consecutive sample, September 2009 – January 2012		
Prognostic variable		**N with event free survival (n=61)**	**N with event (n=43)**
	Normal coronary angiogram	20% (12)	16% (7)
	Atheromatosis	54% (33)	47% (20)
	One vessel	18% (11)	14% (6)
	Two vessel	5% (3)	21% (9)
	Three vessel	3% (2)	2% (1)
	All patients had a thorough clinical work-up, including an electrocardiogram, lung function test, 6-minute walk test, and blood samples including pro-BNP. By September 2013 information on mortality and indication of AVR was obtained from the electronic health record by a systematic review of hospital contacts (outpatient visits and acute admissions) after the baseline examination. The reviewer was blinded to all echocardiographic data. The treating physician was blinded to the results of the echocardiographic examination and the MDCT performed in the present study and referral for AVR was performed independently by the clinical heart team. Cardiac angiography was performed by MDCT with intravenous contrast medium. Coronary computed tomography angiography analyses were performed according to the American Society of Cardiovascular Computed Tomography guidelines. A coronary lesion was considered significant if the stenosis was >50% of the luminal diameter. The American Heart Association 16-segment coronary artery model, modified after Austen et al. was used.		
Confounders	CAD was not reported as adjusted outcome.		

Reference	Carstensen 2016[40]
Outcomes and effect sizes	**43 patients reached the endpoint of indication for AVR** and no patients experienced sudden cardiac death. The indication for AVR was reduced LVEF without symptoms in one patient and symptoms in the rest (n = 42). Median time from baseline examination to indication for AVR was 18 months (IQR 9–28). Seven patients were not operated due to cancer (2), dementia (1), excessive obesity (1), declined (2), and one patient died a sudden cardiac death awaiting AVR. **N with event free survival (n=61)** / **N with event (n=43)** Normal coronary angiogram: 20% (12) / 16% (7) Atheromatosis: 54% (33) / 47% (20) One vessel: 18% (11) / 14% (6) Two vessel: 5% (3) / 21% (9) Three vessel: 3% (2) / 2% (1) Median follow-up of 2.3 years (IQR 1.7–3.6)
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: • None identified

Reference	Larsen 2016[152]
Study type and analysis	Prospective cohort study Multivariable Cox proportional hazards regression model, **but only univariate for our variable of interest**

Reference	Larsen 2016[152]
Number of participants and characteristics	**Total n=116** CAD >70% stenosis on MDCT n = 19 (including 6 with multi-vessel disease) CAD ≤ 70% stenosis on MDCT n = 97 **Inclusion criteria** Asymptomatic aortic stenosis. Asymptomatic defined by the treating physician, with a peak velocity by continuous wave Doppler >2.5 m/s **Exclusion criteria** P-creatinine >130 mmol/l, allergy to contrast, LVEF <50% on echo or known malignant disease **Values listed below are presented as mean (SD), median (IQR) or number (%)** **Patient characteristics:** Age: 72 (8) years Male: 73% Mean AVA by TTE: 1.01 (0.30) cm^2 Current smoker: 16% Past smoker: 57% Systolic blood pressure, mmHg: 145 (20) **Population source**: six hospitals in the Greater Copenhagen area Consecutive sample, September 2009 – January 2012
Prognostic variable	CAD >70% stenosis on MDCT All patients had a thorough clinical work-up, including an electrocardiogram, lung function test, 6-minute walk test, and blood samples including pro-BNP. By September 2013 information on mortality and indication of AVR was obtained from the electronic health record by a systematic review of hospital contacts (outpatient visits and acute admissions) after the baseline examination. The reviewer was blinded to all echocardiographic data.

Reference	Larsen 2016[152]
	The treating physician was blinded to the results of the echocardiographic examination and the MDCT performed in the present study and referral for AVR was performed independently by the clinical heart team. Cardiac angiography was performed by MDCT with intravenous contrast medium. Coronary computed tomography angiography analyses were performed according to the American Society of Cardiovascular Computed Tomography guidelines. A coronary lesion was considered significant if the stenosis was >50% of the luminal diameter. The American Heart Association 16-segment coronary artery model, modified after Austen et al. was used.
Confounders	Univariate Cox regression model only for factors in our protocol
Outcomes and effect sizes	**47 patients reached the endpoint of indication for AVR** and no patients experienced sudden cardiac death. The indication for AVR was reduced LVEF without symptoms in one patient and symptoms in the rest. **Unadjusted hazard ratios for indication for AVR** 1.79 (0.93-3.44) for CAD >70% stenosis vs ≤70% Number with events in prognostic groups not reported and unable to read off reliable estimate from KM curves, as values do not match reported event rate Median follow-up of 27 (IQR 19–44) months
Comments	Risk of bias: 1. Study participation HIGH 2. Study attrition LOW 3. Prognostic factor measurement LOW 4. Outcome Measurement HIGH 5. Study confounding HIGH 6. Statistical analysis HIGH 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH Indirectness: • None identified

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

Reference	Utsunomiya 2013[275]
	• Peak transaortic velocity: 3.75 (1.07) m/s • Peak transaortic velocity ≥4 m/s, 22 (34%) • Mean transaortic pressure gradient: 29 (18) mmHg • Aortic valve area: 1.14 (0.45) cm^2 • Left atrial volume index: 39 (12) ml/m^2 • Septal E/e': 15.2 (6.5) • Lateral E/e': 11.8 (5.3) • CCTA-derived aortic valve area: 1.36 (0.48) cm^2 • CCTA-derived LV ejection fraction: 69 (9)% • CCTA-derived LV mass index: 108 (32) g/m^2 • Multivessel obstructive CAD, 11 (17%) • AVCS, median (IQR): 723 (356-1284) **Population source:** appear to have been enrolled from a single institute. Time period unclear. Unclear if consecutive patients.
Prognostic variable	<u>Whole cohort (asymptomatic mild-severe AS) analyses (n=64)</u> Multi-vessel obstructive CAD No Multi-vessel obstructive CAD (referent) Cardiac CT angiography (CCTA) examinations were performed using multidetector-row CT scanner. Patients with heart rate ≥60 bpm were given an oral beta-blocker to achieve heart rate of 50-60 bpm. Sublingual nitroglycerin administered just before scanning. Dataset of contrast-enhanced scan reconstructed every 5% of R-R interval and transferred to a remote computer workstation. CCTA images were analysed by two experienced observers blinded to clinical and echocardiographic information. Reconstructed images through aortic valve and left ventricle were obtained using 25 cm field of view at 5% intervals throughout the cardiac cycle. <u>CAD</u> Coronary segments ≥2 mm in diameter assessed for obstructive coronary artery disease using thin-slice maximal intensity projections, volume renderings and curved multiplanar reconstructions. Obstructive CAD was defined as ≥50% stenosis or occlusion. If a coronary segment contained multiple lesions, the most severe lesion was recorded.

Reference	Utsunomiya 2013[275]
	CCTA examinations were performed within 1 week of echocardiography.
Confounders	Cox regression analysis performed, with multivariate results available for CAD prognostic factor. Factors included in adjusted analysis: <u>Whole cohort (asymptomatic mild-severe AS):</u> • Multi-vessel obstructive CAD vs. no multi-vessel obstructive CAD: ○ Age (per year), gender, baseline systolic blood pressure (per 10 mmHg), baseline diastolic blood pressure (per 10 mmHg), peak transaortic velocity ≥4 m/s, CCTA-derived aortic valve area (per 0.1 cm^2 decrease), CCTA-derived LV ejection fraction (per 10% decrease), CCTA-derived LV mass index (per 1 SD g/m^2) and AVCS (per 100) Age included in the multivariate results for multi-vessel obstructive CAD prognostic factor, though the other pre-specified confounder in the protocol (smoking) was not adjusted for.
Outcomes and effect sizes	**<u>Cardiac events – cardiac death, aortic valve replacement (AVR), non-fatal myocardial infarction and heart failure requiring urgent hospitalisation</u>** • **HR 2.70 (95% CI 0.95 to 7.65, P=0.063) for multi-vessel obstructive CAD vs. no multi-vessel obstructive CAD – whole cohort (asymptomatic mild-severe AS, n=64) –** adjusted for age, gender, baseline systolic blood pressure, baseline diastolic blood pressure, peak transaortic velocity ≥4 m/s, CCTA-derived aortic valve area, CCTA-derived LV ejection fraction, CCTA-derived LV mass index and AVCS 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]
	Patients were assessed every 6 months during follow-up. Event information was obtained from telephone interviews, contact with patient physicians and hospital records. Coronary revascularisation was not included in cardiac events. Myocardial infarction was defined as typical symptoms, new pathological Q waves on electrocardiogram or elevated serum creatine kinase level. Median (IQR) follow-up for whole cohort: 29 (18-50) months.
Comments	**Cardiac events – cardiac death, aortic valve replacement (AVR), non-fatal myocardial infarction and heart failure requiring urgent hospitalisation** Multi-vessel obstructive CAD vs. no multi-vessel obstructive CAD – whole cohort (asymptomatic mild-severe AS, n=64) Risk of bias: 1. Study participation LOW 2. Study attrition HIGH 3. Prognostic factor measurement LOW 4. Outcome Measurement HIGH 5. Study confounding HIGH 6. Statistical analysis HIGH 7. Other risk of bias LOW OVERALL RISK OF BIAS VERY HIGH Indirectness: • Population – unclear whether all represent a population where it was uncertain whether intervention is required, as includes a mixture of mild-severe asymptomatic AS, with only 45% being asymptomatic severe. • Confounding – though adjustment for one of the confounders pre-specified in the protocol has been performed (age) as well as other factors, the other pre-specified confounder for this outcome (smoking) was not included. Downgraded for this as part of risk of bias rating, so not downgraded further for indirectness. • Outcome – composite outcome consisting of multiple outcomes specified in the protocol, rather than reporting separately.