Appendix D: Clinical evidence tables

Study	**Ahmed 2017[1]**
Study type	Retrospective cohort study
Number of studies (number of participants)	1 (n=300)
Countries and setting	Conducted in USA; Setting: Mixed - retrospective review of medical records
Line of therapy	Not applicable
Duration of study	Other: Medical records reviewed from 25th July 2007 to 6th December 2012
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosed according to current practice guidelines
Stratum	Severe: All have severe asymptomatic aortic stenosis
Subgroup analysis within study	Not applicable
Inclusion criteria	Age ≥18 years; severe aortic stenosis according to current practice guidelines; asymptomatic status, defined as absence of dyspnoea, angina, presyncope and syncope; no prior catheter or surgical aortic valve intervention; no indication for cardiac surgery; and clinical evaluation before 31st December 2012 to enable adequate follow-up duration.
Exclusion criteria	Not reported.
Recruitment/selection of patients	Retrospective review of medical records between 25th July 2007 and 6th December 2012

Age, gender and ethnicity	Age - Mean (SD): Guidelines adherent, 78 (11.6) years; guidelines non-adherent, 79.8 (11.3) years. Gender (M:F): Guidelines adherent, 100/102; guidelines non-adherent, 43/55. Ethnicity: White, 98%; African American, 1.3%; Unknown, 0.7%
Further population details	1. Aortopathy in aortic valve disease: Not stated / Unclear (Not reported). 2. Coronary artery disease: Not stated / Unclear (Mixed - 47.7% with coronary artery disease in the population). 3. Type of valve disease: aortic stenosis (non-bicuspid/calcific) (Note no mention of any with bicuspid/congenital disease but does not state they were excluded either. Based on mean age have classified as non-bicuspid as calcific more commonly affects older people).
Extra comments	Note following factors are written as guideline adherent vs. non-adherent group. Hypertension, 87.6 vs. 84.7%; hyperlipidaemia, 59.4 vs. 48%; diabetes, 27.7 vs. 21.4%; chronic obstructive pulmonary disease, 15.4 vs. 15.3%; malignant neoplasm, 9.9 vs. 8.2%; coronary artery disease, 47.5 vs. 48%; peripheral vascular disease, 14.4 vs. 15.3%; sleep apnoea, 14.9 vs. 15.3%; previous stroke/TIA, 10.4 vs. 8.2%; previous percutaneous coronary intervention, 23.8 vs. 23.5%; previous myocardial infarction, 6.4 vs. 9.2%; previous coronary artery bypass grafting, 22.3 vs. 13.3%; previous sternotomy, 7.4 vs. 10.2%; implantable cardioverter defibrillator, 5.5 vs. 4.1%; permanent pacemaker, 9.4 vs. 13.3%; moderate aortic regurgitation, 16.5 vs. 11%; severe aortic regurgitation, 0.5 vs. 0%; moderate mitral regurgitation, 21.8 vs. 17.7%; severe mitral regurgitation, 2.5% vs. 5.2%%; moderate tricuspid regurgitation, 10.3 vs. 18.8%; severe tricuspid regurgitation, 6.7 vs. 9.4%; median (IQR) creatinine level, 1.06 (0.45) vs. 1.02 (0.41) mg/dL; mean (SD) LVEF, 60 (10) vs. 60 (15)%; mean (SD) STS Mortality Risk score, 3.2 (3.3) vs. 3.3 (2.8); mean (SD) STS Mortality or Morbidity Risk score, 18.8 (10.5) vs. 18.3 (8.4); mean (SD) end-diastolic dimension, 4.5 (1) vs. 4.3 (1) cm; mean (SD) end-systolic dimension, 3 (1.1) vs. 2.9 (1.2) cm; mean (SD) septal wall thickness, 1.3 (0.3) vs. 1.3 (0.5) cm; mean (SD) posterior wall thickness, 1.2 (0.3) vs. 1.2 (0.3) cm; mean (SD) peak aortic velocity, 4 (0.9) vs. 3.9 (1) m/s; mean (SD) integral-derived aortic valve area, 0.78 (0.2) vs. 0.80 (0.29) cm^2; mean (SD) dimensionless index, 0.23 (0.06) vs. 0.22 (0.1); mean (SD) aortic gradient, 37.5 (15.3) vs. 36.1 (16.4) mmHg; mean (SD) cardiac output, 4.9 (17) vs. 4.5 (2) L/min; mean (SD) left atrial volume, 43 (23.5) vs. 43 (27.2) ml; mean (SD) left atrial dimension, 43 (9) vs. 41 (10) mm.
Indirectness of population	No indirectness
Interventions	(n=202) Intervention 1: Imaging - Echocardiography every 12 months. Guideline adherence - defined as serial evaluation occurring every 12 (±6) months until aortic valve replacement or death during the follow-up. Appropriate serial evaluations required the following to be performed: comprehensive clinical evaluation that included description of presence or absence of cardiac symptoms; cardiopulmonary physical examination; and 2D and Doppler echocardiogram including assessment of left ventricular function and the haemodynamic severity of aortic stenosis, with

	documentation of the aortic valve area and either the peak aortic velocity or mean aortic valve gradient. Duration NA. Concurrent medication/care: Not reported. Indirectness: Serious indirectness; Indirectness comment: Monitoring every 12 (+/- 6) months - may not be every 12 months in all cases (n=98) Intervention 2: Imaging - Echocardiography less often than every 12 months. No definition for guideline non-adherence provided - could include those receiving follow-up with all required components more often than every 12 (±6) months, those receiving follow-up with all required components less often than every 12 (±6) months and also those receiving follow-up within 12 (±6) months but without all of the required components (comprehensive clinical review, cardiopulmonary physical examination and 2D and Doppler echocardiogram, as defined for the other group). Duration NA. Concurrent medication/care: Not reported. Indirectness: Serious indirectness; Indirectness comment: No definition of this group in terms of how/when monitoring was performed. Could include follow-up performed more/less often than required by guidelines and also those where follow-up methods (clinical review, echocardiography and cardiopulmonary physical examination) inadequate but within guideline time frame
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RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GUIDELINE ADHERENT GROUP - CLINICAL REVIEW + ECHOCARDIOGRAPHY EVERY 12 (+/- 6) MONTHS] versus GUIDELINE NON-ADHERENT GROUP - NO DETAILS OF MONITORING IN THIS GROUP

Protocol outcome 1: All-cause mortality at 12 months
- Actual outcome for Severe: All-cause mortality at Median (IQR) follow-up duration: 4.5 (2.8-6.5) years; Group 1: n=202 ; Group 2: n=98; HR 0.65; Lower CI 0.44 to Upper CI 0.96. The values reported in the paper (HR 1.54, 95% CI 1.04 to 2.29) were inverted in order to obtain the HR for the guideline adherent group vs. the non-adherent group; Test statistic: 0.03; Follow up details: Median (IQR) follow-up duration: 4.5 (2.8-6.5) years
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Blinding/performance: care received during follow-up period not specified and could have differed between the groups - valve interventions differed substantially between the groups - 54 vs. 19.4%. ; Indirectness of outcome: Serious indirectness, Comments: Adjusted for various factors - including coronary artery disease but not including aortopathy. Unclear whether aortopathy was present within the population as no details provided; Baseline details: Comparable for most of listed factors, but larger differences for some (hyperlipidaemia, AF, previous CABG, moderate tricuspid regurgitation). One of pre-specified confounders adjusted for (coronary artery disease), but other (aortopathy) not mentioned in the study; Key confounders: Coronary artery disease, aortopathy; Group 1 Number missing: no dropouts/missing data reported; Group 2 Number missing: no dropouts/missing data reported.

Protocol outcome 2: Hospitalisation for heart failure or other cardiac reason at 12 months
- Actual outcome for Severe: Hospitalisation for heart failure at Median (IQR) follow-up duration: 4.5 (2.8-6.5) years; Group 1: n=202 ; Group 2: n=98; HR

0.6; Lower CI 0.46 to Upper CI 0.79. The values reported in the paper (HR 1.66, 95% CI 1.27 to 2.18) were inverted in order to obtain the HR for the guideline adherent group vs. the non-adherent group; Test statistic: <0.001; Follow up details: Median (IQR) follow-up duration: 4.5 (2.8-6.5) years Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Blinding/performance: care received during follow-up period not specified and could have differed between the groups. Valve interventions differed substantially between the groups - 54 vs. 19.4%. Measurement: retrospective review of medical records and no definition of outcome - could have been recorded differently for different patients in the database.; Indirectness of outcome: Serious indirectness, Comments: Outcome not adjusted for any baseline variables, though proportion with coronary artery disease at baseline was similar between groups. Aortopathy presence in the population not mentioned.; Baseline details: Comparable for most of listed factors, but larger differences for some (hyperlipidaemia, AF, previous CABG, moderate tricuspid regurgitation). One of pre-specified confounders (coronary artery disease) similar at baseline, but other (aortopathy) not mentioned in the study; Key confounders: Coronary artery disease, aortopathy; Group 1 Number missing: no dropouts/missing data reported; Group 2 Number missing: no dropouts/missing data reported.	
Protocol outcomes not reported by the study	All-cause mortality at 6 months; Cardiac mortality at 12 months; Cardiac mortality at 6 months; Quality of life at 6 months; Quality of life at 12 months; New-onset atrial fibrillation at 12 months; New-onset atrial fibrillation at 6 months