National Institute for Health and Care Excellence

Final

Heart valve disease presenting in adults: investigation and management

[I] Evidence review for repeat intervention for failure of biological or repaired valves

NICE guideline NG208

Evidence reviews underpinning recommendation 1.6.1 and research recommendations in the NICE guideline

November 2021

Final

These evidence reviews were developed by the National Guideline Centre, hosted by the Royal College of Physicians

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1.1 Review question

What is the clinical and cost effectiveness of transcatheter or surgical repeat valve intervention for people with biologic valves or repaired valves that require reintervention due to failure of the valve?

1.1.1 Introduction

All valve intervention options have advantages and disadvantages. Consequently, it is important to determine the clinical and cost effectiveness of each management option compared with each other. It is also important to determine the clinical and cost effectiveness of transcatheter or surgical repeat valve intervention for people with biologic valves or repaired valves that require reintervention.

1.1.2 Summary of the protocol

For full details see the review protocol in Appendix A.

Table 1: PICO characteristics of review question

Population	**Inclusion:** • Adults aged 18 years and over with heart valve disease and repeat valve intervention for biological valve or surgical repair failure • People with either a first or subsequent redo intervention **Stratified by valve position as follows:** • Aortic valve • Mitral valve • Tricuspid valve • Mixed population (i.e. study does not limit to a single type of valve disease – downgrading for indirectness will be considered) **Exclusion:** • Children (aged <18 years). • Adults with congenital heart disease (excluding bicuspid aortic valves). • Re-intervention due to acute endocarditis • Re-intervention for paravalvar regurgitation • Repeat repair intervention
Interventions	Surgical valve replacement with biological or mechanical valve Transcatheter intervention (including TAVI-in- TAVI) *Conventional and minimally invasive, and biological and mechanical surgical valve replacement will be pooled*
Comparisons	Other active comparator listed above Conservative management (for example, medical management/treatment or no treatment)

Outcomes	**Primary** • All-cause mortality at latest reported time-point • Cardiac mortality at latest reported time-point • Intervention-related mortality at 30 days • Health-related quality of life at latest reported time-point • Onset or exacerbation of heart failure at latest reported time-point • Intervention-related stroke or TIA at 30 days • Intervention-related major bleeding at 30 days • Need for reintervention at latest reported time-point **Secondary** • Length of stay (following initial intervention) • Re-hospitalisation at <12 months and ≥12 months • Intervention-related major vascular complications at 30 days (defined as those requiring intervention for a vascular complication)
Study design	Randomised controlled trials (RCTs) or systematic reviews of RCTs If insufficient evidence is found from RCTs, non-randomised studies will be considered for inclusion using the following hierarchy of evidence: • Prospective cohort studies • Retrospective cohort studies. If non-randomised studies are included the following confounders should be accounted for: **Key factor** • Age **Important factors:** • Surgical risk (for example STS score, EuroScore) • Life expectancy • NYHA class • Urgent indication • Ejection fraction (EF) <50% Studies not accounting for age will be excluded. Studies not accounting for surgical risk score or relevant component factors will be downgraded.

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

Seven retrospective cohort studies were included in the review;[3, 6, 35, 47, 49, 51, 60] these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 3 and Table 4).

All of the included studies covered the aortic valve stratum and no evidence was identified for the mitral valve or tricuspid valve strata.

Within the aortic valve stratum, all seven studies covered the same comparison between transcatheter intervention and surgical aortic valve replacement for the redo intervention. In all studies, the previous intervention had been surgical biological valve replacement in the majority of patients – there was only one study (n=350) where one patient had transcatheter intervention as the initial procedure and they had surgical aortic valve replacement as their redo procedure.

As the previous intervention had been surgical biological valve replacement, the transcatheter intervention was often described as transcatheter valve-in-valve or equivalent.

As all studies covered this comparison within the aortic valve stratum, there was no evidence identified for either transcatheter or surgical repeat intervention compared with conservative management (i.e. no treatment or medical management).

No RCTs matching the protocol were identified and the studies that were included were all retrospective cohort studies. For these non-randomised studies to be included, they had to account for differences in age between the two arms of the study. Those that had not accounted for this key confounder either by study design or adjustment were excluded, as pre-specified in the protocol. Other important confounders listed in the protocol were taken into account when assessing risk of bias and any that had not accounted for these were downgraded accordingly.

Five of the studies used matching to generate groups of participants from each treatment arm that could be compared, three of these used propensity scores[3, 35, 51], one matched based on surgical risk score[6], and the other matched only based on age[49]. The remaining two studies[47, 60] did not perform matching, but data was available for one outcome where they had performed multivariate analysis adjusting for age and other variables.

Inconsistency

Though inconsistency was identified for some outcomes (intervention-related stroke or TIA and major vascular complications), pre-specified subgroup analyses could not explain the heterogeneity. For the stroke outcome, this was because all four studies reporting this outcome were within the same categories for all pre-specified subgroups. For the major vascular complications outcome there were not enough studies included in the meta-analysis to perform subgroup analyses as only two studies reported this outcome, which would mean at least one of the subgroups would have only one or fewer studies in.

As there was unexplained heterogeneity for both of these outcomes, the results for each study are presented separately rather than being pooled. The results for the stroke outcome are presented as Peto odds ratios due to there being zero events in at least one arm or a <1% event rate in each of the studies.

Though there was some indication of inconsistency for a third outcome (intervention-related major bleeding), based on the point estimates, this was not considered to be inconsistency that required studies to be analysed separately or downgraded as the point estimates of all

three studies were in favour of the transcatheter intervention. Though one study[35] also reported transfusion as an outcome, the more general postoperative haemorrhage that the same study reported was included in the analysis, as not all major bleeding events may have required transfusion and transfusion may have also been performed for reasons other than bleeding.

Intervention-related mortality outcome

For this outcome, where possible only events that appeared to be intervention-related were extracted. However, if this was not possible, any mortality within 30 days was included under the outcome, as most of the studies only provided details of all-cause mortality within this short time-period. This was not downgraded for indirectness as due to the short time period it was still thought to be applicable to the outcome specified.

See also the study selection flow chart in Appendix C, study evidence tables in Appendix D, forest plots in Appendix E and GRADE tables in Appendix F.

1.1.4.2 Excluded studies

See the excluded studies list in Appendix J.

1.1.5 Summary of studies included in the effectiveness evidence

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Deharo 2020[3] Retrospective cohort study N=1434 France	**Transcatheter aortic valve-in-valve replacement (n=717):** valve-in-valve transcatheter procedure performed as redo operation. Balloon-expandable in 46.7% and self-expandable in 53.3%. Details of concurrent care not reported. **Redo surgical aortic valve replacement (n=717):** redo surgical aortic valve replacement performed. No further details on type of valve used (biological or mechanical) or invasiveness of surgery.	Those hospitalised with a diagnosis of aortic stenosis as principal, related or significantly associated diagnosis, with a surgically implanted bioprosthetic valve requiring reintervention (for regurgitation or stenosis) and ≥18 years of age Included those between January 2010 and June 2019 Confounders Mean age: transcatheter, 74.9 (9.7) years; surgery, 74.5 (8.2) years.	Mortality at mean 794 days Cardiovascular mortality at mean 794 days All-cause mortality at 30 days Onset or exacerbation of heart failure (hospitalisation for heart failure) at mean 794 days All-cause stroke at 30 days Major or life-threatening bleeding at 30 days	Accounted for age as propensity-score matching was performed to produce groups that could be compared, including age and other variables.

Study	Intervention and comparison	Population	Outcomes	Comments
	Details of concurrent care not reported.	Mean EuroSCORE II score: 4.70 (1.0) vs. 4.70 (1.0) NYHA class, ejection fraction, life expectancy and proportion with urgent indication not reported Exclusion criteria: Age <18 years, other not reported.		
Ejiofor 2016[6] Retrospective cohort study N=44 USA	**Transcatheter aortic valve-in-valve replacement (n=22):** first option was transfemoral approach, with transaortic, transapical and subclavian approaches alternatives if iliofemoral vessels not adequate. Edwards Sapien, Edwards Sapien XT or Medtronic CoreValve used **Redo surgical aortic valve replacement with biological or mechanical valve (n=22):** minimally invasive procedure through upper hemi-sternotomy was performed where possible and full sternotomy where it was not (68.2% minimally invasive and 32.8% full sternotomy). Patients received biological (81.8%; Carpentier-Edwards Magna/Pericardial	Previously received surgical bioprosthetic valve and undergoing subsequent redo aortic valve procedure Included those undergoing redo procedures between 2012 and 2016 Confounders Mean age: transcatheter, 73.7 (10.4) years; surgical, 73.3 (8.6) years Data for other important confounders not provided. Exclusion criteria: Hospitalisation with concomitant diagnoses of other valve disease Hospitalisation with diagnosis of endocarditis Missing data for age, sex, length of stay or death	Operative mortality Postoperative permanent stroke Reintervention due to paravalvular leakage Hospital length of stay Intensive care unit length of stay Readmission at 30 days	Accounted for age as matching was performed based on surgical risk score (STS PROM) to select groups of patients that could be compared

Study	Intervention and comparison	Population	Outcomes	Comments
	or Sorin Mitroflow) or mechanical valves (18.2%; St. Jude).			
Malik 2020[35] Retrospective cohort study N=1420 USA	**Transcatheter aortic valve-in-valve replacement (n=710):** transcatheter valve-in-valve procedure, no details regarding type of valve or access route. **Redo surgical aortic valve replacement (n=710):** redo surgical aortic valve replacement performed. No information on type of valve used (biological or mechanical) or invasiveness of surgery.	Previously received surgical bioprosthetic valve and undergoing subsequent redo aortic valve procedure Included those undergoing redo procedures between 2012 and 2016 <u>Confounders</u> Mean age: transcatheter, 73.7 (10.4) years; surgical, 73.3 (8.6) years Data for other important confounders not provided. <u>Exclusion criteria:</u> Hospitalisation with concomitant diagnoses of other valve disease Hospitalisation with diagnosis of endocarditis Missing data for age, sex, length of stay or death	In-hospital mortality In-hospital postoperative haemorrhage Hospital length of stay – only means with no SD In-hospital vascular complications	Limited to in-hospital outcomes Accounted for age and other variables by use of propensity score matching The odds ratios reported in this study had wider confidence intervals than those calculated using the number of events in each group, but it was unclear how this had been calculated in the report. Therefore, effect estimates calculated manually using number of events were used.
Sedeek 2019[47] Retrospective cohort study N=350 USA	**Transcatheter aortic valve-in-valve replacement (n=90):** Transcatheter valve-in-valve procedure. Arterial access was through femoral artery in 88% (n=79), left ventricular apex in 11% (n=10) and	Those with failing surgical aortic bioprosthetic valves (apart from one patient in the redo surgical group that initially received a TAVI valve) undergoing a redo intervention	All-cause mortality at median 2.1 years (IQR 1.2-4.2 years) - HR	Accounted for age and other variables as performed multivariable analysis including age, STS PROM score and internal aortic prosthesis diameter for the mortality outcome. Other outcomes without adjustment

Study	Intervention and comparison	Population	Outcomes	Comments
	innominate artery in 1% (n=1). Valves used were Sapien S3 in 33% (n=30), Sapein XT in 31% (n=28), Sapien in 2% (n=2), Evolut in 28% (n=25) and CoreValve in 6% (n=5). **Redo surgical aortic valve replacement with biological or mechanical valves (n=260):** redo surgical aortic valve replacement performed. All but 1 had surgical bioprosthetic valves previously, the remaining patient received a TAVI valve at the initial operation. No information on the invasiveness of surgery. Type of valve used: stented bioprosthesis, 57%; mechanical prosthesis, 39%; and stentless bioprosthesis, 4%. Concomitant procedures were performed in 30% of patients (n=79): mitral valve operation, 20% (n=53); tricuspid valve operation, 12% (n=30); and other cardiac procedures, 21% (n=55)	Included those matching criteria between November 2008 and May 2018 <u>Confounders</u> Median (IQR) age: transcatheter, 79 (76-83) years; surgical, 72 (63-77) years Median (IQR) STS PROM score: 7.5 (4.9-10.7)% vs. 3.0 (2.1-5.3)% NYHA class III or IV: 83% vs. 62% Non-elective operative status: 28% vs. 23% Median (IQR) ejection fraction: 0.56 (0.45-62) vs. 0.62 (0.55-0.66) Life expectancy not reported <u>Exclusion criteria:</u> None reported		were not extracted as age differs between groups.
Silaschi 2017[49] Retrospective cohort study N=130	**Transcatheter aortic valve-in-valve replacement (n=71):** Transcatheter valve-in-valve procedure. Edwards Sapien valves used in	Those with failing aortic surgical bioprosthesis undergoing repeat intervention Those matching criteria between 2008 and 2015 for	All-cause mortality up to 1 year – HR Cardiac mortality at 30 days Intervention-related mortality at 30 days	Accounted for age as selected matched groups to analyse based on age and procedure received. Not as well matched as other studies for age and other variables, but has

Study	Intervention and comparison	Population	Outcomes	Comments
Germany and UK	50.7% (n=36), CoreValve used in 39.5% (n=28), St. Jude Portico valve used in 4.2% (n=3), Medtronic Engager valve used in 2.8% (n=2) and JenaValve used in 2.8% (n=2). Access was transapical in 46.5% (n=33), transvascular in 49.3 (n=35) and transaortic in 4.2% (n=3). **Redo surgical aortic valve replacement with biological valves (n=59):** redo surgical aortic valve replacement performed. Bioprostheses were used for the redo replacement in all patients, which were stented in 94.9% (n=56) and stentless in 5.1% (n=3). Invasiveness of surgery unclear	transcatheter and 2002 and 2015 for surgical intervention <u>Confounders</u> Mean age: transcatheter, 78.6 (7.5) years; surgical, 72.9 (6.6) years Mean Logistic EuroSCORE: 25.1 (18.9)% vs. 16.8 (9.3)% LVEF: 30-50%: 7% vs. 22% <30%: 8.5% vs. 5.1% NYHA class, life expectancy and proportion with urgent indication not reported <u>Exclusion criteria:</u> Not reported	Non-disabling or disabling stroke at 30 days Life-threatening or disabling bleeding at 30 days ICU length of stay Re-hospitalisation at 180 days Major vascular complications at 30 days	attempted to account for age.
Spaziano 2017[51] Retrospective cohort study N=156 Belgium, Canada, Denmark, France, Germany and Italy	**Transcatheter aortic valve-in-valve replacement (n=78):** Transcatheter valve-in-valve procedure, termed TAVI-in-SAVR. Transcatheter valves used were CoreValve in 59% (n=46) and Edwards valves (Sapien, Sapien XT or Sapien 3) in 41% (n=32). Access route was transfemoral in 54% (n=42), transapical in 31% (n=24) and other in 15% (n=12). Conversion to open heart surgery did	Those with failing surgical bioprosthetic valves undergoing repeat intervention Those matching criteria between January 2007 and January 2015 at any of the centres <u>Confounders</u> Mean age: transcatheter, 78.0 (8.0) years; surgical, 77.4 (5.0) years Mean logistic EuroSCORE:	All-cause mortality at 1 year – HR Mortality at 30 days Stroke at 30 days Total hospital length of stay	Age was accounted for by use of propensity score matching to select groups for comparison, including age and other variables.

Study	Intervention and comparison	Population	Outcomes	Comments
	not occur in any patients and a second transcatheter valve was required in 5.1% (n=4) of patients. N=33 (42%) had coronary artery disease that required revascularisation. Percutaneous coronary intervention was performed prior to TAVI-in-SAVR in n=32 patients and during the TAVI-in-SAVR procedure in n=1 patient **Redo surgical aortic valve replacement with biological valves (n=78):** redo surgical aortic valve replacement. Bioprosthetic valves were used in all cases for the redo operation. These were stented in 99% (n=77) and stentless in 1% (n=1). Invasiveness of surgery unclear. N=25 (32%) patients underwent either coronary artery bypass grafting (n=21) or percutaneous coronary intervention (n=4) concomitantly at the time of surgery due to coronary artery disease that required revascularisation.	22.1 (16.0) vs. 22.1 (18.3) STS score: 7.2 (4.9) vs. 5.8 (4.6) NYHA class III or IV: 72% vs. 88% Urgent procedure: 6% vs. 13% Mean LVEF: 50.7 (13.5)% vs. 49.5 (13.4)% Life expectancy not reported. <u>Exclusion criteria:</u> Reason for redo replacement was paravalvular leak, valve endocarditis or valve thrombosis		
Woitek 2020[60]	**Transcatheter aortic valve-in-valve replacement (n=147):** valve-in-	Those with degenerated surgical aortic bioprosthetic	All-cause mortality at 12 months - HR	Accounted for age and other variables as performed multivariable

Study	Intervention and comparison	Population	Outcomes	Comments
Retrospecti ve cohort study N=258 Germany	valve transfemoral transcatheter aortic valve implantation. Preoperative CT scan performed in all patients in this group. 2.1% had percutaneous coronary intervention within the same hospital stay and 4.1% had coronary artery disease that was treated medically. **Redo surgical aortic valve replacement with biological valves (n=111):** redo surgical aortic valve replacement by sternotomy. 18.9% received a mechanical valve. Experienced consultant cardiac surgeons performed all redo-sternotomies and operations. Preoperative CT scans were performed in 94.6% in this group. 27% had concurrent surgery on the thoracic aorta, 0.9% had mitral valve decalcification, 9.0% had the Morrow procedure, 12.6% had concomitant coronary bypass grafting, 0.9% had percutaneous coronary intervention during the same hospital stay and 2.7% had coronary artery	valves undergoing repeat intervention Those matching criteria between January 2006 and May 2017 <u>Confounders</u> Mean age: transcatheter, 76.2 (8.0) years; surgical, 58.5 (14.4) years STS-PROM score: 8.27 (6.12)% vs. 2.76 (2.09)% NYHA class III or IV: 72.8% vs. 46.4% Mean LVEF: 54.5 (13.9)% vs. 57.4 (10.2)% Life expectancy and proportion of urgent procedures not reported. <u>Exclusion criteria:</u> Those undergoing surgical redo operation because the transcatheter procedure was not possible		analysis for the mortality outcome. Unclear exactly which variables are included in the final model, but may include: age, NYHA class III or IV at baseline, sex, STS-PROM, coronary artery disease at baseline and mode of failure (regurgitation). Other outcomes without adjustment were not extracted as age differs between groups.

Study	Intervention and comparison	Population	Outcomes	Comments
	disease that was treated medically.			

See Appendix D for full evidence tables.

1.1.6 Summary of the effectiveness evidence

Aortic valve

Table 3: Clinical evidence summary: Evidence not suitable for GRADE analysis – transcatheter valve-in-valve vs. redo surgical aortic valve replacement for those with failing aortic bioprosthetic valves

Study	Intervention and comparator	Outcome	Intervention results	Intervention group (n)	Comparator results	Comparator group (n)	P-value	Risk of bias
Ejiofor 2016[6]	Transcatheter valve-in-valve vs. redo surgical aortic valve replacement	Intensive care unit length of stay	Median (IQR): 0 (0-50) hours	22	Median (IQR): 68 (43-98) hours	22	0.001	Very high
Ejiofor 2016[6]	Transcatheter valve-in-valve vs. redo surgical aortic valve replacement	Hospital length of stay	Median (IQR): 5 (2-7) days	22	Median (IQR): 10.5 (8-18) days	22	0.001	Very high
Malik 2020[35]	Transcatheter valve-in-valve vs. redo surgical aortic valve replacement	Hospital length of stay	Mean: 6.6 days (SD not reported so could not be analysed)	710	Mean: 9.6 days (SD not reported so could not be analysed)	710	<0.01	Very high
Spaziano 2017[51]	Transcatheter valve-in-valve vs. redo surgical aortic valve replacement	Hospital length of stay	Median (IQR): 9 (7-13) days	78	Median (IQR): 12 (8-24) days	78	0.001	Very high

Table 4: Clinical evidence summary: transcatheter valve-in-valve vs. redo surgical aortic valve replacement for those with failing aortic bioprosthetic valve

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with redo surgical aortic valve replacement	Risk difference with transcatheter valve-in-valve (95% CI)
All-cause mortality at latest reported time-point - HR	894 (4 studies) 1-2 years	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	HR 1.12 (0.69 to 1.81)	146 per 1000	16 more per 1000 (from 43 fewer to 102 more)
All-cause mortality at latest reported time-point - dichotomous	1434 (1 study) 794 days	⨁⊖⊖⊖ VERY LOW [a,b] due to risk of bias, imprecision	RR 1.16 (0.95 to 1.41)	205 per 1000	33 more per 1000 (from 10 fewer to 84 more)
Cardiac mortality at latest reported time-point	1564 (2 studies) 30-794 days	⨁⊖⊖⊖ VERY LOW [a,b] due to risk of bias, imprecision	RR 1.03 (0.77 to 1.38)	80 per 1000	2 more per 1000 (from 18 fewer to 30 more)
Intervention-related mortality at 30 days	3184 (5 studies) operative/ in-hospital - 30 days	⨁⨁⊖⊖ LOW [a] due to risk of bias	RR 0.37 (0.25 to 0.53)	51 per 1000	40 fewer per 1000 (from 50 fewer to 20 fewer)3
Health-related quality of life at latest reported time-point	Not reported				
Onset or exacerbation of heart failure at latest reported time-point	1434 (1 study) 794 days	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 1.38 (1.15 to 1.67)	201 per 1000	76 more per 1000 (from 30 more to 135 more)
Intervention-related stroke or TIA at 30 days – 4 studies unpooled due to unexplained heterogeneity					
Deharo 2020[3]: All-cause stroke at 30 days	1434 (1 study) 30 days	⨁⊖⊖⊖ VERY LOW[a,b,d] due to risk of bias, imprecision	OR 2.24 (0.65 to 7.76)	4 per 1000	5 more per 1000 (from 1 fewer to 27 more)
Ejiofor 2016[6]: Postoperative permanent stroke	44 (1 study) postoperative	⨁⊖⊖⊖ VERY LOW[a,b,d,e] due to risk of bias, indirectness, imprecision	OR 0.13 (0.01 to 2.13)	91 per 1000	91 fewer per 1000 (from 231 fewer to 50 more)[c]

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with redo surgical aortic valve replacement	Risk difference with transcatheter valve-in-valve (95% CI)
Silaschi 2017[49]: Non-disabling or disabling stroke at 30 days	130 (1 study) 30 days	⨁⊖⊖⊖ VERY LOW[a,b,d] due to risk of bias, imprecision	OR 0.11 (0.01 to 1.78)	34 per 1000	34 fewer per 1000 (from 88 fewer to 20 more)[c]
Spaziano 2017[51]: Stroke according to VARC-2 at 30 days	156 (1 study) 30 days	⨁⊖⊖⊖ VERY LOW[a,b,d] due to risk of bias, imprecision	OR 7.39 (0.15 to 372.38)	0 per 1000	13 more per 1000 (from 22 fewer to 48 more)[c]
Intervention-related major bleeding at 30 days	2984 (3 studies) in-hospital-30 days	⨁⊖⊖⊖ VERY LOW[a,b,f] due to risk of bias, indirectness, imprecision	RR 0.57 (0.37 to 0.87)	310 per 1000	133 fewer per 1000 (from 40 fewer to 195 fewer)
Need for reintervention at latest reported time-point (reintervention due to paravalvular leakage)	44 (1 study) unclear	⨁⊖⊖⊖ VERY LOW[a,h,i] due to risk of bias, indirectness, imprecision	RD 0 (-0.08 to 0.08)	0 per 1000	0 fewer per 1000 (from 80 fewer to 80 more)[g]
Length of stay (following initial redo intervention)	Data not reported in format that could be analysed and presented in separate table above.				
ICU length of stay (following initial redo intervention)	130 (1 study) postoperative	⨁⊖⊖⊖ VERY LOW[a,b,j] due to risk of bias, imprecision		The mean ICU length of stay (following initial redo intervention) in the control groups was 3.4 days	The mean ICU length of stay (following initial redo intervention) in the intervention groups was 1.4 lower (2.25 to 0.55 lower)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with redo surgical aortic valve replacement	Risk difference with transcatheter valve-in-valve (95% CI)
Rehospitalisation at <12 months postoperatively - 30-180 days	141 (2 studies) 30-180 days	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 1.88 (0.68 to 5.23)	88 per 1000	77 more per 1000 (from 28 fewer to 372 more)
Rehospitalisation at ≥12 months	Not reported				
Intervention-related major vascular complications at 30 days – 2 studies unpooled due to unexplained heterogeneity					
Malik 2020[35]: Intervention-related major vascular complications (those requiring intervention) - in-hospital	1420 (1 study) in-hospital	⨁⊖⊖⊖ VERY LOW[a,b,k,l] due to risk of bias, indirectness, imprecision	RR 0.53 (0.23 to 1.25)	21 per 1000	10 fewer per 1000 (from 16 fewer to 5 more)
Silaschi 2017[49]: Intervention-related major vascular complications (VARC-2 definition) at 30 days	130 (1 study) 30 days	⨁⊖⊖⊖ VERY LOW[a,b,k] due to risk of bias, imprecision	RR 2.49 (0.71 to 8.79)	51 per 1000	76 more per 1000 (from 15 fewer to 397 more)

[a]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[b]Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[c]Risk difference used to manually calculate absolute effect as one study with zero events in one arm.
[d]For this outcome, the point estimate of two studies was in opposite direction to the other two studies. Prespecified subgrouping strategies could not explain these differences so results were not pooled. Differences may be due to small event numbers in all studies. Studies therefore kept separate rather than pooling.
[e]Unclear whether includes all of those up to 30 days as time-point is unclear
[f]One of the studies (79.8% weighting) defined the outcome as postoperative haemorrhage - unclear whether this covered the whole 30 day period specified in the protocol and also may include non-major bleeding events.
[g]Risk difference used to manually calculate absolute effect as zero events in both arms of a single study.
[h]Outcome poorly defined as only states that none required reintervention for paravalvular leakage - may have been other reasons that did require intervention but not reported. Time-point also unclear - may have covered immediate postoperative period only or 3 year follow-up.
[i]Assessment of imprecision based on sample size as zero events in both arms. Very serious imprecision as sample size <70.
[j]MIDs used to assess imprecision were ±1.45
[k]For this outcome, the point estimate of one study in opposite direction to the other study. Subgroup analyses could not be performed as only two studies. Studies therefore kept separate rather than pooling.
[l]Limited to in-hospital and does not necessarily cover 30 day time period in all patients. Also unclear whether all events were events that required intervention.

See Appendix F for full GRADE tables.

Mitral valve

No evidence identified.

Tricuspid valve

No evidence identified.

1.1.7 Economic evidence

1.1.7.1 Included studies

No health economic studies were included.

1.1.7.2 Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in Appendix G.

1.1.9 Economic model

This area was not prioritised for new cost-effectiveness analysis.

1.1.10 Unit costs

Relevant unit costs are provided below to aid consideration of cost effectiveness.

Resource	Unit costs (Procedure and valve)	Source
TAVI low-risk	£28,085	NHS Reference Costs and Supply Chain Catalogue 2018* [40, 41]
TAVI intermediate-risk	£29,938	NHS Reference Costs and Supply Chain Catalogue 2018* [40, 41]
TAVI high-risk	£32,259	NHS Reference Costs and Supply Chain Catalogue 2018* [40, 41]
SAVR low-risk	£15,246	NHS Reference Costs* [40, 41]
SAVR intermediate-risk	£17,640	NHS Reference Costs* [40, 41]
SAVR high-risk	£21,940	NHS Reference Costs* [40, 41]

*The cost of the procedure was calculated using NHS Reference Costs excluding the length of stay component. The cost of length of stay and ICU was calculated using the data from the trials included in the clinical review [34] [32] [50] and added back to the procedure cost. For TAVI, the cost of the valve reported by the Supply Chain Catalogue was added to the overall cost.

1.1.11 Evidence statements

Effectiveness

- See the summary of evidence in Table 3 and Table 4.
- Three studies reported the median and interquartile range, or the mean without standard deviation, for hospital and/or intensive care unit length of stay and could not be assessed in GRADE. Weak evidence from 3 RCTs[6,35,51] (n=1620) suggested a reduced length of stay in hospital or ICU in the transcatheter group compared to the surgery group for adults having redo surgical aortic valve replacement.

Economic

- No relevant economic evaluations were identified.

1.1.12 The committee's discussion and interpretation of the evidence

1.1.12.1. The outcomes that matter most

Outcomes considered to be critical as listed in the protocol were all-cause mortality at latest reported time-point, cardiac mortality at latest reported time-point, intervention-related mortality at 30 days, health-related quality of life at latest reported time-pint, onset or exacerbation of heart failure at latest reported time-point, intervention-related stroke or TIA at 30 days, intervention-related major bleeding at 30 days and need for reintervention at latest reported time-point.

The following three additional outcomes were listed in the protocol as important outcomes: length of stay (following the intervention), rehospitalisation at <12 months and ≥12 months, and intervention-related major vascular complications at 30 days.

All evidence identified was for a single comparison within the aortic valve stratum (transcatheter vs. surgery for redo aortic valve replacement). Within this comparison,

evidence from non-randomised, retrospective studies was identified for most of the listed outcomes, though for a number of outcomes this was only from a single study. Outcomes that were not reported in any of the included studies were as follows: health-related quality of life at any time-point and re-hospitalisation at ≥12 months.

No evidence was identified for the mitral or tricuspid valve disease strata, or for comparisons between transcatheter or surgical redo intervention and conservative or no treatment within the aortic valve disease stratum.

1.1.12.2 The quality of the evidence

Strata and comparisons covered

No relevant studies were identified for the following strata included in the protocol: mitral valve disease and tricuspid valve disease. Research recommendations were made for evidence comparing transcatheter and surgical repeat intervention options in these populations (see Appendix K.2.1 and K.3.1 for details). Research recommendations were not prioritised for the comparison with conservative or no treatment as where there is an indication for repeat intervention this research was thought to be less feasible given ethical considerations.

In addition, though there were seven studies included for the aortic valve disease stratum, all of these covered the same comparison between transcatheter and surgical intervention for redo aortic valve replacement, meaning there was no evidence for either transcatheter or surgical redo intervention vs. conservative management or no treatment. Research recommendations were not prioritised for the comparison with conservative or no treatment as where there is an indication for repeat intervention this research was thought to be less feasible given ethical considerations.

The included studies differed in terms of their sample size, with two larger studies with >1000 participants included, four with sample sizes between 100 and 350 participants and the remaining study having fewer than 50 participants included. Despite some studies being very small, a large number of participants were analysed for most reported outcomes within meta-analyses, with the majority having at least 1000 participants included.

Study design and confounding

All included evidence was obtained from non-randomised, retrospective cohort studies. Evidence from non-randomised studies is more limited than evidence from RCTs due to increased issues with selection bias and potential differences between groups contributing to the effects observed, making it difficult to interpret how much of the effect is due to the different interventions received and how much is due to other differences that exist between groups as a result of the selection process. In these studies, assignment to a specific treatment is likely to have been based patient characteristics and the opinion of the medical team treating them. If a particular treatment is thought to be a higher risk for patients that have certain characteristics, then groups may become unbalanced as this treatment is avoided in people with those characteristics. However, if studies have accounted for these confounders as part of the analysis, for example through using matched populations or statistical adjustment of results, this is less of an issue.

During protocol development, the committee agreed that age was a key confounder that should be accounted for in all studies included in the review. Therefore, only studies that had accounted for age, either through matching processes or statistical adjustment of results, would be included in the review and those that had not would be excluded. Other important confounders were also specified in the protocol: surgical risk, life expectancy, NYHA class, urgent indication and ejection fraction <50%. Studies did not have to account for these to be included, but the presence or absence of methods to account for these additional factors was used to inform the risk of bias rating for confounding factors.

Although all included studies had accounted for age differences between the two study arms, some studies did not report information on any of the other important confounders specified in the protocol and in other studies differences in some of these characteristics were observed between groups and had not been accounted for. For example, in four studies the proportion with NYHA class III/IV symptoms differed substantially between the transcatheter and surgery groups (95.5% vs. 72.7%, 83% vs. 62%,72% vs. 88%, and 72.8% vs. 46.4%, respectively). In another study, the proportion with an ejection fraction ≤50% differed between the two arms and was not accounted for (15.5% vs. 27.1%). In the remaining two studies, all of the patient characteristics that were reported appeared to be well matched, but they did not report data for many of the confounders in the protocol other than age, so it is unclear whether the two groups were also similar for these characteristics.

In addition to confounders listed in the protocol, within the individual studies there were other differences observed between the treatment arms. For example, in one study there were differences in the proportion with renal failure, a history of cerebrovascular accident and previous coronary artery bypass grafting in transcatheter and surgery groups. This differed for each study, although in most cases there was a higher proportion of a particular risk factor in the transcatheter arm compared with the surgery arm.

Quality of outcomes

The quality of all but one outcome included in this review was rated very low, with the remaining outcome (intervention-related mortality at 30 days) being graded low quality. As discussed in the previous section under 'study design and confounding', selection bias in non-randomised studies and the issue of some confounding factors not being accounted for in the analysis, which was a component of the risk of bias assessment, was one factor that contributed to this rating for all outcomes.

In addition, imprecision was also an issue for a lot of the outcomes, including all-cause mortality, cardiac mortality, onset or exacerbation of heart failure, intervention-related stroke, intervention-related major bleeding, need for reintervention, intensive care unit length of stay, rehospitalisation and intervention-related major vascular complications. Confidence intervals were very wide for most of these outcomes, with very serious imprecision identified for all-cause mortality, cardiac mortality, intervention-related stroke, need for reintervention, rehospitalisation and intervention-related major vascular complications outcomes as both MIDs were crossed or, in the case of need for reintervention, based on sample size as there were zero events in both arms of a single study and sample size was <70 participants. Serious imprecision was noted for onset or exacerbation of heart failure, intervention-related major bleeding and intensive care unit length of stay, based on one MID being crossed. In some cases imprecision was caused by studies suggesting opposing directions of effect and/or a low number of events, but the small sample sizes of some meta-analyses may also have contributed to this for some outcomes.

Indirectness was also a reason for downgrading a number of outcomes. In most cases this was because the time-point the outcome was reported at was shorter than the minimum specified in the protocol as ideal (for example, cardiac mortality was reported at 30 days rather than the minimum of 3 months and in some studies only in-hospital results were reported for the 30-day outcomes of intervention-related mortality, intervention-related major bleeding, intervention-related stroke or TIA and intervention-related major vascular complications).

Inconsistency was identified for intervention-related stroke or TIA and major vascular complications. Pre-specified subgroup analyses could not explain the inconsistency, as there were either not enough studies to perform the analyses or all of the studies fell into the same subgrouping categories. The results were therefore presented separately for each study rather than pooling.

The committee highlighted that the absence of RCTs in this area is a limitation and though non-randomised evidence was included in the review, agreed that this was insufficient to be able to recommend one treatment over the other. Participants assigned to the transcatheter arm were likely to differ in characteristics compared to those assigned to the surgery arm, which may contribute to any differences observed between the groups.

As all included evidence comparing transcatheter redo intervention with surgical redo intervention covered those with failing biological prosthetic aortic valves, recommendations involving transcatheter redo intervention were limited to this population, as there was no included evidence to support a recommendation in mitral or tricuspid valve disease. Based on the limitations associated with non-randomised evidence, as well as the small number of participants included in most studies and a lack of data longer than 12 months follow-up, the strength of the recommendations made was therefore limited to “consider” and a research recommendation for an RCT within this population was made with the aim of strengthening the evidence available for this comparison in the future (see Appendix K.1 for details). Research recommendations were also made for evidence comparing transcatheter and surgical repeat intervention options in the mitral and tricuspid valve disease populations (see Appendix K.2.1 and K.3.1 for details). Research recommendations were not prioritised for the comparison with conservative or no treatment for any of the three populations as where there is an indication for repeat intervention this research was thought to be less feasible given ethical considerations.

1.1.12.3 Benefits and harms

Across the seven studies included in this review, comparing transcatheter intervention with surgery for redo aortic valve replacement, some clinically important benefits of transcatheter intervention over surgery were identified. In addition, some potential clinically important harms and outcomes where no clinically important difference was observed were identified, however there was much more uncertainty for these outcomes, based on the confidence intervals around the absolute effect being consistent with more than one conclusion (for example, an absolute effect suggesting a harm but the confidence intervals also being consistent with no clinically important difference, or even a clinically important benefit),compared with those where a clinically important benefit was observed.

<u>Outcomes suggesting a benefit of transcatheter intervention</u>

Outcomes that indicated a benefit of transcatheter over surgical intervention for redo aortic valve replacement were intervention-related mortality, intervention-related major bleeding and hospital and intensive care unit length of stay. For hospital and intensive care unit length of stay, this judgement was based on data reported in both table 3 and table 4.

A clinically important benefit was observed for intervention-related mortality with fairly narrow confidence intervals and no uncertainty in the conclusion as confidence intervals were also consistent with a clinically important benefit. A similar result was observed for intervention-related major bleeding, though only 3 studies reported this outcome and there was some uncertainty in this conclusion as the lower confidence interval for the absolute effect suggested there could also be no clinically important difference between the groups. For both outcomes evidence was graded low or very low quality.

Though only 2 studies reported a length of stay outcome in a format that could be analysed using GRADE and presented as a forest plot, other studies reported the median and interquartile range, or the mean without standard deviation, for hospital and/or intensive care unit length of stay. Across all 3 studies that reported data for hospital length of stay and the 2 studies that reported data for intensive care unit length of stay, all of them suggested reduced length of stay in the transcatheter group compared to the surgery group, meaning it was concluded that a benefit was identified for this outcome. However, the fact that only 1 study reported the results in a format that could be analysed by GRADE meant that an absolute effect could not be calculated for all of this evidence combined, making it difficult to

assess the uncertainty in this effect and the size of the effect, so it was unclear whether the effect was clinically important. As with other included evidence, those reporting the outcomes in a format that could not be analysed by GRADE were considered to be at very high risk of bias.

Outcomes suggesting a harm of transcatheter intervention

There were four outcomes (all-cause mortality, cardiac mortality, onset or exacerbation of heart failure at 1-2 years, and rehospitalisation <3 months postoperatively) where the absolute effect suggested a clinically important harm of transcatheter intervention compared to surgery; however, uncertainty was present based on the confidence intervals surrounding the absolute effect estimate, as described below for each outcome.

Although the absolute effect for all-cause mortality for time-to-event and dichotomous results, cardiac mortality and rehospitalisation <12 months postoperatively suggested a clinically important harm of transcatheter intervention, the confidence intervals around the absolute effects were wide, meaning there was uncertainty in the result and whether there was a clinically important benefit, clinically important harm or no clinically important difference. In addition, this was based on very low quality evidence for all outcomes. For all-cause mortality, within the meta-analysis of time-to-event data, one study suggested a benefit of transcatheter intervention while the others suggested a harm; however, all studies had wide confidence intervals demonstrating uncertainty in the effect across all studies. For cardiac mortality, one study reported the outcome at a time-point of only 30 days, whereas ideally data at a time-point of at least 3 months would be preferred for this outcome. For the rehospitalisation outcome, the results were based on only 141 participants across the 2 studies. Therefore, there is a lot of uncertainty present in the results for these two outcomes. Only one study reported data for onset or exacerbation of heart failure, with the results suggesting a clinically important harm of the transcatheter intervention in terms of the absolute effect. However, there was some uncertainty as to whether the difference was clinically important based on confidence intervals as the lower confidence interval of the absolute effect was consistent with no clinically important difference between the groups. In addition, the results were only based on a single study, with evidence being graded low quality.

Outcomes suggesting no difference or where there is heterogeneity

There were three outcomes (intervention-related stroke, need for reintervention and major vascular complications), where no difference between the two groups was suggested or where heterogeneity was present, based on the absolute effect estimates that were calculated. Results for these outcomes are limited due to small event numbers in some studies and heterogeneity between studies for two of these outcomes, meaning there is uncertainty in the true effect, and it is difficult to conclude whether or not there is an effect of the treatment group on outcome and what the direction of any effect is. For all of these outcomes evidence was graded very low quality.

For the intervention-related stroke and major vascular complications outcomes, unexplained heterogeneity was observed and the results were therefore presented separately for each study. Each of these outcomes had one study that suggested a clinically important difference (benefit for stroke, harm for major vascular complications) between the two groups based on the absolute effect. However, in both cases there was uncertainty in this conclusion as confidence intervals were also consistent with no clinically important difference. For both outcomes, the remaining study or studies suggested no clinically important difference between the groups based on the absolute effect. There was uncertainty in this conclusion for one of the studies reporting stroke based on confidence intervals around the absolute effect also being consistent with a clinically important benefit, but the confidence intervals for the others were also consistent with no clinically important difference, which was also the case for the other study reporting major vascular complications. For the studies reporting stroke, there were zero events in at least one arm of three of the four studies, and a <1%

event rate in the fourth study, with three of the four studies also having small sample sizes (<200 participants), contributing to the uncertainty that exists as to the true effect.

For the need for reintervention outcome, only one study reported this and defined it as 'reintervention for paravalvular leakage' – there were zero events in both arms leading to the conclusion that there was no clinically important difference between the two groups. The confidence interval around the absolute effect estimate indicated uncertainty in this conclusion as it was consistent with a clinically important harm and clinically important benefit, as well as no clinically important difference as suggested by the absolute effect. As this is only based on a single study with 22 participants in each group and uncertainty based on the confidence intervals, the evidence is too limited to be sure that there is no difference between the groups for this outcome.

Summary

Based on the absolute effects, or a judgement based on all available data for length of stay outcomes, some clinically important benefits of transcatheter intervention were observed, as well as some clinically important harms. For other outcomes the absolute effects indicated no clinically important difference between groups. However, for most of these outcomes there was uncertainty in terms of the size and/or direction of effect. For a further two studies different studies suggested different directions of effect, making it difficult to make a conclusion based on absolute effects. It was agreed that there is a lack of information for longer term outcomes.

The committee agreed that although potential benefits and harms of transcatheter redo intervention compared with surgical redo intervention were identified for those with failing biological prosthetic aortic valves, the limitations highlighted in the evidence, which include uncertainty for many outcomes and those described under 'the quality of the evidence', mean there is insufficient evidence to be able to favour one over the other, but agreed that transcatheter did appear to be a suitable procedure for some patients. For example, redo intervention is more common in older adults where transcatheter intervention may be clinically indicated.

A recommendation to consider either transcatheter or redo surgical intervention for adults with severe aortic degeneration of a biological prosthetic valve and symptoms, with the decision to be based on the short and long-term benefits, type of valve dysfunction and prosthesis, the risks associated with the procedure and the possible need for any other cardiac procedures in the future in a shared-decision making process. The term degenerated refers to progressive degeneration and does not include failure of the valve due to endocarditis or thrombosis. It was noted that the longevity of transcatheter and surgical valves is thought to differ, with surgical valves likely to last longer before a further repeat intervention is required, which is why it is important to take the short and long-term benefits into account in the decision. For risks associated with the procedure, those with higher operative risks may be at increased risk of adverse outcomes following surgery and transcatheter redo intervention may therefore be preferable, whereas surgery might be deemed more appropriate for those who require other concomitant cardiac interventions. In terms of the type of valve dysfunction and prosthesis, this may also affect the decision as, for example, some prostheses may be too small for a transcatheter redo procedure to be performed. The decision between options should be based on a discussion of all of these factors with each individual patient.

The recommendation was limited to those with severe aortic degeneration of a biological prosthetic valve and symptoms, as it was highlighted that not every patient with valve degeneration requires intervention immediately and this group represents those with an indication for repeat intervention. As degeneration of biological prosthetic aortic valves is progressive and usually occurs over a couple of decades, the valve can continue to function well with mild degeneration and redo intervention would not be performed in these cases, as is the case with mild native valve disease. Although it was noted that indications for repeat

intervention are less well-defined currently compared to those for a first heart valve intervention in those with native heart valve disease it was noted that in general, redo intervention is usually needed in those where the degeneration of the prosthetic valve results in stenosis and/or regurgitation that is progressive and severe enough to cause symptoms. For this reason, the recommendation was made in those with severe aortic degeneration of a biological prosthetic valve and symptoms.

Despite no evidence comparing transcatheter redo intervention with medical management in those with failing bioprosthetic aortic valves, the committee agreed that transcatheter redo intervention should be considered in those where surgery was not suitable, as the included evidence suggested that transcatheter procedure is a suitable option for some patients and noted that without intervention, patients treated medically may remain symptomatic and may deteriorate and die prematurely.

Based on the limitations of non-randomised evidence, and the lack of evidence identified for mitral and tricuspid valve disease, research recommendations for RCTs covering comparisons between transcatheter redo intervention and surgical redo intervention for those with biological prosthetic valves were also made. It was acknowledged that mitral and tricuspid repeat valve intervention are much smaller areas compared with repeat aortic valve intervention, with fewer numbers of patients. For this reason, research recommendations included non-randomised comparative studies with appropriate accounting of confounding. The aim of these research recommendations is to improve the strength of the evidence available to base recommendations on for these comparisons in the future. Research recommendations were not prioritised for the comparison with conservative or no treatment as where there is an indication for repeat intervention this research was thought to be less feasible given ethical considerations.

1.1.12.4 Cost effectiveness and resource use

There was no published cost effectiveness evidence. The committee were presented with the unit costs of transcatheter and surgical interventions.

Despite no studies included comparing intervention with no intervention, the committee noted that the outcome for these patients with a failing biological valve without reintervention is very poor based on their clinical experience. The evidence shows good outcomes from surgery and therefore redo surgery is likely to be cost effective in suitable patients.

These patients are older than at the time of first surgery and redo surgery carries important additional risks. TAVI was found to be a cost effective first-line intervention for inoperable patients (See Evidence Review H). TAVI therefore is a reasonable treatment if technically feasible for selected patients where redo surgery has a very high operative risk or is not possible.

The committee noted that surgical valves are likely to last longer before a further repeat intervention is required, and therefore should be favoured for patients with longer life expectancy which would reduce the number of repeat interventions.

The committee highlighted that patients in need of concomitant cardiac interventions would benefit from surgery as more than one cardiac issue can be resolved in one surgery. This would reduce the costs of further interventions and result in improved clinical and quality of life outcomes.

A consensus recommendation was made in line with current practice to consider either transcatheter or surgical re-intervention depending on the patient's life expectancy, operative risk, need for any other cardiac procedures and patient preferences. As this recommendation was based on current practice it should not result in a resource impact.

1.1.12.5 Other factors the committee took into account

The committee were unable to make consensus recommendations for the remaining strata and comparisons due to the absence of evidence and the variation in current clinical practice.

The committee highlighted that it is considered best practice for decisions on when to perform interventions and which intervention to perform to be made as part of a multidisciplinary heart team. However, it was also noted that in practice, the use of these varies. As the review did not investigate the evidence for decision-making by a multidisciplinary team a recommendation in this regard was not made.

The committee noted that lifestyle (work, caring responsibilities, social life) was an important contributing factor for patients when making decisions on what treatment to have.

1.1.13 Recommendations supported by this evidence review

This evidence review supports recommendations 1.6.1 and the 3 research recommendations on repeat intervention.

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Appendices

Appendix A – Review protocols

Review protocol for repeat intervention for failure of biological or repaired valves

ID	Field	Content
0.	PROSPERO registration number	CRD42020182846
1.	Review title	What is the clinical and cost effectiveness of transcatheter or surgical repeat valve intervention for people with biologic valves or repaired valves that require reintervention due to failure of the valve?
2.	Review question	What is the clinical and cost effectiveness of transcatheter or surgical repeat valve intervention for people with biologic valves or repaired valves that require reintervention due to failure of the valve?
3.	Objective	To assess and compare the clinical and cost-effectiveness of surgical valve replacement and transcatheter intervention for people with biologic valves or repaired valves that require reintervention due to failure of the valve.
4.	Searches	The following databases (from inception) will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE Searches will be restricted by: • English language • Human studies

		• Letters and comments are excluded • Validated study filters for systematic reviews and RCTs • No date restrictions applied Other searches: • Inclusion lists of systematic reviews will be checked by the reviewer The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review.
5.	Condition or domain being studied	Diagnosed heart valve disease in adults aged 18 years and over: Aortic (including bicuspid) stenosis, aortic regurgitation, mitral stenosis, mitral regurgitation and tricuspid regurgitation.
6.	Population	Inclusion: • Adults aged 18 years and over with heart valve disease and repeat valve intervention for biological valve or surgical repair failure • People with either a first or subsequent redo intervention Stratified by valve position as follows: • Aortic valve • Mitral valve • Tricuspid valve • Mixed population (i.e study does not limit to a single type of valve disease – downgrading for indirectness will be considered)

		Exclusion: • Children (aged <18 years). • Adults with congenital heart disease (excluding bicuspid aortic valves). • Re-intervention due to acute endocarditis • Re-intervention for paravalvar regurgitation • Repeat repair intervention
7.	Intervention	Surgical valve replacement with biological or mechanical valve Transcatheter intervention (including TAVI-in- TAVI) *Conventional and minimally invasive, and biological and mechanical surgical valve replacement will be pooled*
8.	Comparator	Other active comparator listed above Conservative management (for example, medical management/treatment or no treatment)
9.	Types of study to be included	Randomised controlled trials (RCTs) or systematic reviews of RCTs If insufficient[1] evidence is found from RCTs, non-randomised studies will be considered for inclusion using the following hierarchy of evidence: • Prospective cohort studies • Retrospective cohort studies.

[1] This will be assessed for the review as a whole. There is no strict definition, but in discussion with the GC we will consider whether we have enough to form the basis for a recommendation (e.g., one large well-conducted RCT, or more than one small RCT).

		If non-randomised studies are including the following confounders should be accounted for: Key factor • Age Important factors: • Surgical risk (for example STS score, EuroScore) • Life expectancy • NYHA class • Urgent indication • Ejection fraction (EF) <50% Studies not accounting for age will be excluded. Studies not accounting for surgical risk score or relevant component factors will be downgraded.
10.	Other exclusion criteria	Exclusion criteria: • Conference abstracts will be excluded because they are unlikely to contain enough information to assess whether the population matches the review question in terms of previous medication use, or enough detail on outcome definitions, or on the methodology to assess the risk of bias of the study. • Non-English language studies
11.	Context	Replaced biologic or repaired heart valves often deteriorate and require re-intervention. It is not known whether standard surgery or transcatheter methods should be preferred in this scenario.
12.	Primary outcomes (critical outcomes)	• All-cause mortality at latest reported time-point • Cardiac mortality at latest reported time-point

		• Intervention-related mortality at 30 days • Health-related quality of life at latest reported time-point • Onset or exacerbation of heart failure at latest reported time-point • Intervention-related stroke or TIA at 30 days • Intervention-related major bleeding at 30 days • Need for reintervention at latest reported time-point Follow-up: • Pool outcomes reported at the time-points specified above
13.	Secondary outcomes (important outcomes)	• Length of stay (following initial intervention) • Re-hospitalisation at <12 months and ≥12 months • Intervention-related major vascular complications at 30 days (defined as those requiring intervention for a vascular complication) Follow-up: • Pool outcomes reported at the time-points specified above and take the latest reported time-point for the ≥12 months' time-point if multiple time points reported in a single study
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. An in-house developed database; EviBase, will be used for data extraction. A standardised form is followed to extract data from studies (see Developing NICE

		guidelines: the manual section 6.4) and for undertaking assessment of study quality. Summary evidence tables will be produced including information on: study setting; study population and participant demographics and baseline characteristics; details of the intervention and control interventions; study methodology' recruitment and missing data rates; outcomes and times of measurement; critical appraisal ratings.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0) • Non randomised study, including cohort studies: Cochrane ROBINS-I 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
16.	Strategy for data synthesis	• EndNote will be used for reference management, sifting, citations and bibliographies. • EviBASE will be used for data extraction and quality assessment for clinical studies. • MS Excel will be used for data extraction and critical appraisal for health economic studies.

		• Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). • GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ • WinBUGS will be used for network meta-analysis, if possible given the data identified. Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome.	
17.	Analysis of sub-groups	**Groups that will be analysed separately (strata):** Population • Type of valve originally operated on (aortic, mitral, tricuspid, multiple, mixed) **Subgroups that will be investigated if heterogeneity is present:** • Age (<75 versus ≥75 years) • TAVI in TAVI (versus other transcatheter re-intervention) Studies will be assigned to different subgroups using a threshold of 75% if there is a mixed population.	
18.	Type and method of review	☒	Intervention
		☐	Diagnostic

		☐	Prognostic	
		☐	Qualitative	
		☐	Epidemiologic	
		☐	Service Delivery	
		☐	Other (please specify)	
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	09/05/2019		
22.	Anticipated completion date	17/06/2021		
23.	Stage of review at time of this submission	Review stage	Started	Completed
		Preliminary searches	☑	☑
		Piloting of the study selection process	☑	☑
		Formal screening of search results against eligibility criteria	☑	☑
		Data extraction	☑	☑
		Risk of bias (quality) assessment	☑	☑
		Data analysis	☑	☑
24.	Named contact	5a. Named contact National Guideline Centre		

		5b Named contact e-mail HVD@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre
25.	Review team members	From the National Guideline Centre: Sharon Swain [Guideline lead] Eleanor Samarasekera [Senior systematic reviewer] Nicole Downes [Systematic reviewer] George Wood [Systematic reviewer] Robert King [Health economist] Jill Cobb [Information specialist] Katie Broomfield [Project manager]
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a

		meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.	
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10122	
29.	Other registration details	None	
30.	Reference/URL for published protocol		
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	Aortic regurgitation; Aortic stenosis; Biological heart valve; Heart valve disease; Heart valve replacement; Intervention; Mitral regurgitation; Mitral stenosis; Repeat intervention; Surgical valve replacement; Transcatheter valve replacement; Tricuspid regurgitation	
33.	Details of existing review of same topic by same authors	N/A	
34.	Current review status	☐	Ongoing
		☒	Completed but not published
		☐	Completed and published

		☐	Completed, published and being updated
		☐	Discontinued
35.	Additional information	N/A	
36.	Details of final publication	www.nice.org.uk	

Table 5: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2004, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[38] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).

	• OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2004 or later that depend on unit costs and resource data entirely or predominantly from before 2004 will be rated as 'Not applicable'. • Studies published before 2004 will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B Literature search strategies

Heart valve disease – search strategy 8 - transcatheter intervention, surgery or conservative management

This literature search strategy was used for the following review:

- What is the clinical and cost-effectiveness of transcatheter intervention, surgery (with mechanical or biological valves) and conservative management compared with each other for adults with heart valve disease?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[38]

For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 6: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 - 14 October 2020	Exclusions Randomised controlled trials Systematic review studies
Embase (OVID)	1974 - 14 October 2020	Exclusions Randomised controlled trials Systematic review studies
The Cochrane Library (Wiley)	Cochrane Reviews to 2020 Issue 10 of 12 CENTRAL to 2020 Issue 10 of 12	None

Medline (Ovid) search terms

1.	exp valvular heart disease/
2.	exp heart valve/
3.	((primary or secondary) adj valv* disease*).ti,ab.
4.	((valv* or flap* or leaflet*) adj1 (heart or cardiac) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)).ti,ab.
5.	((mitral or aortic or tricuspid or pulmon*) adj (valv* or flap* or leaflet*) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)).ti,ab.
6.	((mitral or aortic or tricuspid or pulmon*) adj3 (prolapse or regurgitation or stenos?s or atresia or insufficienc*)).ti,ab.
7.	exp heart valve prosthesis/
8.	((mechanical or artificial or prosthe* or bioprosthe* or biological or tissue) adj (valv* or flap* or leaflet*)).ti,ab.
9.	valve-in-valve.ti,ab.
10.	(transcatheter adj2 (valve or valves)).ti,ab.
11.	exp heart murmur/
12.	((heart or cardiac) adj murmur*).ti,ab.
13.	or/1-12
14.	letter.pt. or letter/
15.	note.pt.
16.	editorial.pt.
17.	Case report/ or Case study/
18.	(letter or comment*).ti.
19.	or/14-18
20.	randomized controlled trial/ or random*.ti,ab.
21.	19 not 20

22.	animal/ not human/
23.	Nonhuman/
24.	exp Animal Experiment/
25.	exp Experimental animal/
26.	Animal model/
27.	exp Rodent/
28.	(rat or rats or mouse or mice).ti.
29.	or/21-28
30.	13 not 29
31.	limit 30 to English language
32.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
33.	31 not 32
34.	random*.ti,ab.
35.	factorial*.ti,ab.
36.	(crossover* or cross over*).ti,ab.
37.	((doubl* or singl*) adj blind*).ti,ab.
38.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
39.	crossover procedure/
40.	single blind procedure/
41.	randomized controlled trial/
42.	double blind procedure/
43.	or/34-42
44.	systematic review/
45.	meta-analysis/
46.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
47.	((systematic or evidence) adj3 (review* or overview*)).ti,ab.
48.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
49.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
50.	(search* adj4 literature).ab.
51.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
52.	((pool* or combined) adj2 (data or trials or studies or results)).ab.
53.	cochrane.jw.
54.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
55.	or/44-53
56.	33 and (43 or 55)
57.	exp heart surgery/
58.	exp valvular heart disease/su [Surgery]
59.	exp heart valve prosthesis/ or exp heart valve replacement/
60.	exp catheterization/
61.	exp minimally invasive surgery/
62.	((transcatheter or surg* or intervention*) adj3 (repair* or replac* or implant*)).ti,ab.
63.	(TAVR or TAVI or TMVR or TMVI).ti,ab.
64.	((cardiovascular or cardiac or heart or robotic) adj2 surg*).ti,ab.

65.	(commissurotomy or valvulotomy or valvotomy or valvuloplasty or valvoplasty or annuloplasty).ti,ab.
66.	(sternotomy or ministernotomy or mini-sternotomy or thoracotomy or port access or non-sternotomy).ti,ab.
67.	(mitra clip or MitraClip or edge to edge or chord* or balloon).ti,ab.
68.	or/57-67
69.	56 and 68

Embase (Ovid) search terms

1.	exp valvular heart disease/
2.	exp heart valve/
3.	((primary or secondary) adj valv* disease*).ti,ab.
4.	((valv* or flap* or leaflet*) adj1 (heart or cardiac) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)).ti,ab.
5.	((mitral or aortic or tricuspid or pulmon*) adj (valv* or flap* or leaflet*) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)).ti,ab.
6.	((mitral or aortic or tricuspid or pulmon*) adj3 (prolapse or regurgitation or stenos?s or atresia or insufficienc*)).ti,ab.
7.	exp heart valve prosthesis/
8.	((mechanical or artificial or prosthe* or bioprosthe* or biological or tissue) adj (valv* or flap* or leaflet*)).ti,ab.
9.	valve-in-valve.ti,ab.
10.	(transcatheter adj2 (valve or valves)).ti,ab.
11.	exp heart murmur/
12.	((heart or cardiac) adj murmur*).ti,ab.
13.	or/1-12
14.	letter.pt. or letter/
15.	note.pt.
16.	editorial.pt.
17.	Case report/ or Case study/
18.	(letter or comment*).ti.
19.	or/14-18
20.	randomized controlled trial/ or random*.ti,ab.
21.	19 not 20
22.	animal/ not human/
23.	Nonhuman/
24.	exp Animal Experiment/
25.	exp Experimental animal/
26.	Animal model/
27.	exp Rodent/
28.	(rat or rats or mouse or mice).ti.
29.	or/21-28
30.	13 not 29
31.	limit 30 to English language
32.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
33.	31 not 32
34.	random*.ti,ab.

35.	factorial*.ti,ab.
36.	(crossover* or cross over*).ti,ab.
37.	((doubl* or singl*) adj blind*).ti,ab.
38.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
39.	crossover procedure/
40.	single blind procedure/
41.	randomized controlled trial/
42.	double blind procedure/
43.	or/34-42
44.	systematic review/
45.	meta-analysis/
46.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
47.	((systematic or evidence) adj3 (review* or overview*)).ti,ab.
48.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
49.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
50.	(search* adj4 literature).ab.
51.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
52.	((pool* or combined) adj2 (data or trials or studies or results)).ab.
53.	cochrane.jw.
54.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
55.	or/44-53
56.	33 and (43 or 55)
57.	exp heart surgery/
58.	exp valvular heart disease/su [Surgery]
59.	exp heart valve prosthesis/ or exp heart valve replacement/
60.	exp catheterization/
61.	exp minimally invasive surgery/
62.	((transcatheter or surg* or intervention*) adj3 (repair* or replac* or implant*)).ti,ab.
63.	(TAVR or TAVI or TMVR or TMVI).ti,ab.
64.	((cardiovascular or cardiac or heart or robotic) adj2 surg*).ti,ab.
65.	(commissurotomy or valvulotomy or valvotomy or valvuloplasty or valvoplasty or annuloplasty).ti,ab.
66.	(sternotomy or ministernotomy or mini-sternotomy or thoracotomy or port access or non-sternotomy).ti,ab.
67.	(mitra clip or MitraClip or edge to edge or chord* or balloon).ti,ab.
68.	or/57-67
69.	56 and 68

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Heart Valve Diseases] explode all trees
#2.	MeSH descriptor: [Heart Valves] explode all trees
#3.	((primary or secondary) NEXT valv* disease*):ti,ab
#4.	((valv* or flap* or leaflet*) near/1 (heart or cardiac) NEXT (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)):ti,ab

#5.	((mitral or aortic or tricuspid or pulmon*) NEXT (valv* or flap* or leaflet*) NEXT (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)):ti,ab
#6.	((mitral or aortic or tricuspid or pulmon*) NEAR/3 (prolapse or regurgitation or stenos?s or atresia or insufficienc*)):ti,ab
#7.	MeSH descriptor: [Heart Valve Prosthesis] explode all trees
#8.	((mechanical or artificial or prosthe* or bioprosthe* or biological or tissue) NEXT (valv* or flap* or leaflet*)):ti,ab
#9.	valve-in-valve:ti,ab
#10.	(transcatheter NEAR/2 (valve or valves)):ti,ab
#11.	MeSH descriptor: [Heart Murmurs] explode all trees
#12.	((heart or cardiac) NEXT murmur*):ti,ab
#13.	(or #1-#12)
#14.	MeSH descriptor: [Cardiac Surgical Procedures] explode all trees
#15.	MeSH descriptor: [Heart Valve Diseases] explode all trees and with qualifier(s): [surgery - SU]
#16.	MeSH descriptor: [Heart Valve Prosthesis Implantation] explode all trees
#17.	MeSH descriptor: [Catheterization] explode all trees
#18.	MeSH descriptor: [Minimally Invasive Surgical Procedures] explode all trees
#19.	((transcatheter or surg* or intervention*) near/3 (repair* or replac* or implant*)):ti,ab
#20.	(TAVR or TAVI or TMVR or TMVI):ti,ab
#21.	((cardiovascular or cardiac or heart or robotic) near/2 surg*):ti,ab
#22.	(commissurotomy or valvulotomy or valvotomy or valvuloplasty or valvoplasty or annuloplasty):ti,ab
#23.	(sternotomy or ministernotomy or mini-sternotomy or thoracotomy or port access or non-sternotomy):ti,ab
#24.	(mitra NEXT clip or MitraClip or "edge to edge" or chord* or balloon):ti,ab
#25.	(or #14-#24)
#26.	#13 and #25

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to heart valve disease population in NHS Economic Evaluation Database (NHS EED) – (this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) – (this ceased to be updated after March 2018) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics.

Table 7: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	01 January 2014 – 15 October 2020	Exclusions Health economics studies
Embase	01 January 2014 – 15 October 2020	Exclusions Health economics studies
Centre for Research and Dissemination (CRD)	HTA - Inception – 31 March 2018 NHSEED - Inception to 31 March 2015	None

Medline (Ovid) search terms

1.	exp Heart Valve Diseases/
2.	exp heart valves/
3.	((primary or secondary) adj valv* disease*).ti,ab.
4.	((valv* or flap* or leaflet*) adj1 (heart or cardiac) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)).ti,ab.
5.	((mitral or aortic or tricuspid or pulmon*) adj (valv* or flap* or leaflet*) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)).ti,ab.
6.	((mitral or aortic or tricuspid or pulmon*) adj3 (prolapse or regurgitation or stenos?s or atresia or insufficienc*)).ti,ab.
7.	Heart Valve Prosthesis/
8.	((mechanical or artificial or prosthe* or bioprosthe* or biological or tissue) adj (valv* or flap* or leaflet*)).ti,ab.
9.	valve-in-valve.ti,ab.
10.	(transcatheter adj2 (valve or valves)).ti,ab.
11.	exp Heart Murmurs/
12.	((heart or cardiac) adj murmur*).ti,ab.
13.	or/1-12
14.	letter/
15.	editorial/
16.	news/
17.	exp historical article/
18.	Anecdotes as Topic/
19.	comment/
20.	case report/
21.	(letter or comment*).ti.
22.	or/14-21
23.	randomized controlled trial/ or random*.ti,ab.
24.	22 not 23
25.	animals/ not humans/
26.	exp Animals, Laboratory/
27.	exp Animal Experimentation/
28.	exp Models, Animal/
29.	exp Rodentia/
30.	(rat or rats or mouse or mice).ti.
31.	or/24-30
32.	13 not 31
33.	limit 32 to English language
34.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
35.	33 not 34
36.	Economics/
37.	Value of life/

38.	exp "Costs and Cost Analysis"/
39.	exp Economics, Hospital/
40.	exp Economics, Medical/
41.	Economics, Nursing/
42.	Economics, Pharmaceutical/
43.	exp "Fees and Charges"/
44.	exp Budgets/
45.	budget*.ti,ab.
46.	cost*.ti.
47.	(economic* or pharmaco?economic*).ti.
48.	(price* or pricing*).ti,ab.
49.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
50.	(financ* or fee or fees).ti,ab.
51.	(value adj2 (money or monetary)).ti,ab.
52.	or/36-51
53.	35 and 52

Embase (Ovid) search terms

1.	exp valvular heart disease/
2.	exp heart valve/
3.	((primary or secondary) adj valv* disease*).ti,ab.
4.	((valv* or flap* or leaflet*) adj1 (heart or cardiac) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)).ti,ab.
5.	((mitral or aortic or tricuspid or pulmon*) adj (valv* or flap* or leaflet*) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)).ti,ab.
6.	((mitral or aortic or tricuspid or pulmon*) adj3 (prolapse or regurgitation or stenos?s or atresia or insufficienc*)).ti,ab.
7.	exp heart valve prosthesis/
8.	((mechanical or artificial or prosthe* or bioprosthe* or biological or tissue) adj (valv* or flap* or leaflet*)).ti,ab.
9.	valve-in-valve.ti,ab.
10.	(transcatheter adj2 (valve or valves)).ti,ab.
11.	exp heart murmur/
12.	((heart or cardiac) adj murmur*).ti,ab.
13.	or/1-12
14.	letter.pt. or letter/
15.	note.pt.
16.	editorial.pt.
17.	Case report/ or Case study/
18.	(letter or comment*).ti.
19.	or/14-18
20.	randomized controlled trial/ or random*.ti,ab.
21.	19 not 20
22.	animal/ not human/
23.	Nonhuman/

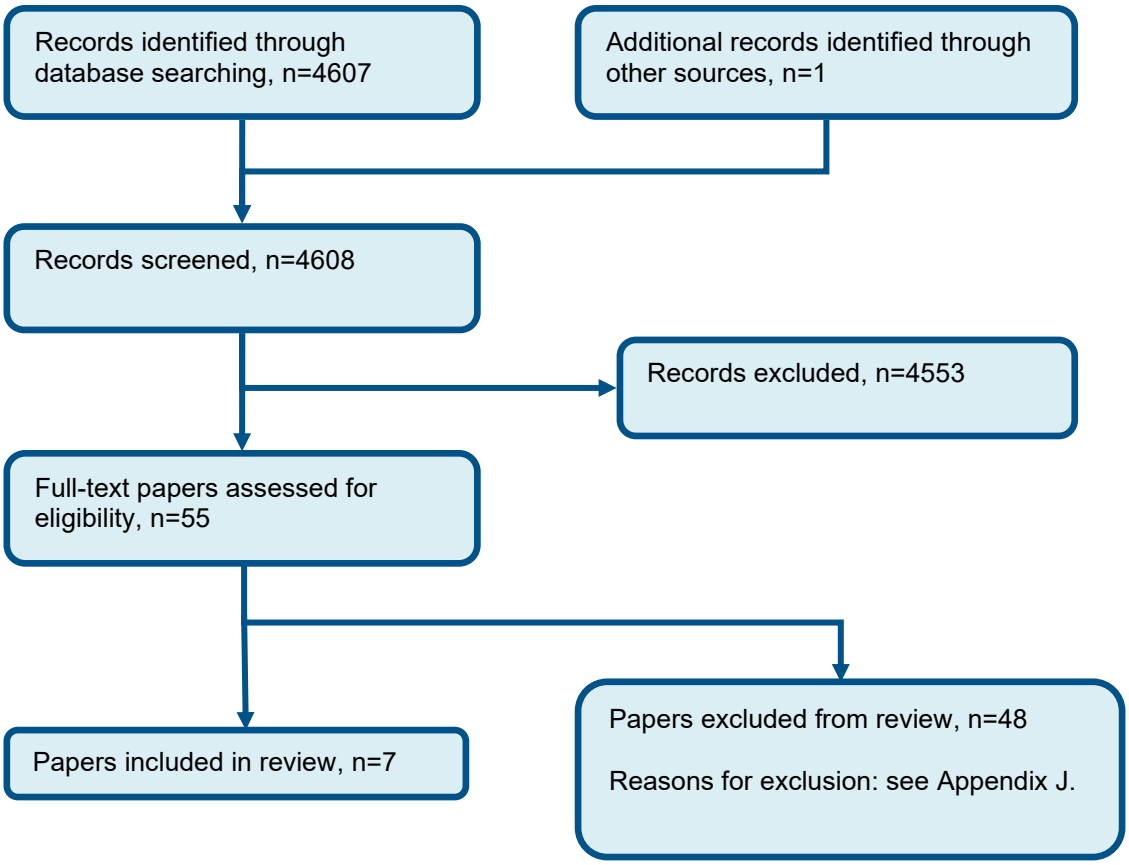
24.	exp Animal Experiment/
25.	exp Experimental animal/
26.	Animal model/
27.	exp Rodent/
28.	(rat or rats or mouse or mice).ti.
29.	or/21-28
30.	13 not 29
31.	limit 30 to English language
32.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
33.	31 not 32
34.	health economics/
35.	exp economic evaluation/
36.	exp health care cost/
37.	exp fee/
38.	budget/
39.	funding/
40.	budget*.ti,ab.
41.	cost*.ti.
42.	(economic* or pharmaco?economic*).ti.
43.	(price* or pricing*).ti,ab.
44.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
45.	(financ* or fee or fees).ti,ab.
46.	(value adj2 (money or monetary)).ti,ab.
47.	or/34-46
48.	33 and 47

NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Heart Valve Diseases EXPLODE ALL TREES
#2.	MeSH DESCRIPTOR Heart Valves EXPLODE ALL TREES
#3.	(((primary or secondary) adj Valv* adj disease*))
#4.	(((valv* or flap* or leaflet*) adj (heart or cardiac) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)))
#5.	((heart or cardiac) adj (valv* or flap* or leaflet*) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*))
#6.	(((mitral or aortic or tricuspid or pulmon*) adj (valv* or flap* or leaflet*) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)))
#7.	(((mitral or aortic or tricuspid or pulmon*) adj3 (prolapse or regurgitation or stenos?s or atresia or insufficienc*)))
#8.	MeSH DESCRIPTOR Heart Valve Prosthesis EXPLODE ALL TREES
#9.	(((mechanical or artificial or prosthe* or bioprosthe* or biological or tissue) adj (valv* or flap* or leaflet*)))
#10.	(valve-in-valve)
#11.	((transcatheter adj2 (valve or valves)))
#12.	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11

Appendix C – Effectiveness evidence study selection

Figure 1: Flow chart of clinical study selection for the review of repeat intervention for failure of biological or repaired valves



Appendix D – Effectiveness evidence

Study	Deharo 2020[3]
Study type	Retrospective cohort study
Number of studies (number of participants)	1 (n=4327 (1434 in propensity-matched population))
Countries and setting	Conducted in France; Setting: Secondary care
Line of therapy	2nd line
Duration of study	Intervention + follow up: Mean (SD) follow-up post-redo intervention was 760 (795) days in unmatched population and 794 (675) days in matched cohort.
Method of assessment of guideline condition	Unclear method of assessment/diagnosis: Unclear how diagnosis was confirmed initially but likely to have been echocardiography
Stratum	Aortic valve: Those with aortic stenosis and a history of surgically implanted aortic bioprosthesis requiring reintervention with either transcatheter or surgical aortic valve replacement.
Subgroup analysis within study	Not applicable:
Inclusion criteria	Adults ≥18 years; hospitalised with diagnosis of aortic stenosis as principal diagnosis, related diagnosis or a significantly associated diagnosis; history of surgically implanted aortic bioprosthesis requiring reintervention (for regurgitation or stenosis) either by transcatheter or isolated surgical aortic valve replacement.
Exclusion criteria	Age <18 years.
Recruitment/selection of patients	Those matching inclusion criteria included in database between 1st January 2010 and 30th June 2019
Age, gender and ethnicity	Age - Mean (SD): VIV TAVR, 74.9 (9.7) years; redo SAVR, 74.5 (8.2) years. Gender (M:F): VIV TAVR, 402/315; redo SAVR, 414/303. Ethnicity: Not reported

Further population details	1. Age: Age ≥75 years (Mean age in both groups is ~75 years).
Extra comments	Those with prior surgical bioprosthetic aortic valves. Charlson comorbidity index, mean (SD): 4.7 (3.0) vs. 4.5 (3.1); frailty index, mean (SD): 9.7 (8.7) vs. 9.2 (8.3); EuroSCORE II, mean (SD): 4.7 (1.0) vs. 4.7 (1.0); hypertension, 79.4% vs. 77.8%; diabetes mellitus, 31.7% vs. 30.3%; heart failure, 65.8% vs. 66.1%; history of pulmonary oedema, 16.0% vs. 12.8%; aortic regurgitation, 31.1% vs. 30.7%; mitral regurgitation, 26.5% vs. 25.0%; previous endocarditis, 9.2% vs. 9.3%; dilated cardiomyopathy, 16.9% vs. 17.0%; coronary artery disease, 56.9% vs. 57.0%; previous myocardial infarction, 14.6% vs. 14.9%; previous percutaneous coronary intervention, 14.4% vs. 13.5%; previous coronary artery bypass grafting, 24.8% vs. 22.3%; vascular disease, 37.1% vs. 36.7%; atrial fibrillation, 61.2% vs. 60.8%; previous pacemaker or defibrillator, 22.3% vs. 21.2%; ischaemic stroke, 5.3% vs. 5.0%; intracranial bleeding, 1.5% vs. 1.3%; smoker, 13.8% vs. 15.2%; dyslipidaemia, 54.1% vs. 52.9%; obesity, 30.4% vs. 28.0%; abnormal renal function, 15.9% vs. 15.2%; lung disease, 26.9% vs. 25.9%; COPD, 16.3% vs. 15.9%; liver disease, 8.4% vs. 7.0%; thyroid diseases, 14.4% vs. 14.1%; inflammatory disease, 9.3% vs. 10.7%; anaemia, 38.6% vs. 36.5%
Indirectness of population	No indirectness
Interventions	(n=717) Intervention 1: Transcatheter intervention (including TAVI-in-TAVI). Valve-in-valve transcatheter procedure performed as redo intervention. Balloon-expandable TAVR performed in 46.7% and self-expandable TAVR performed in 53.3%. Duration NA - transcatheter intervention. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Type of transcatheter intervention: Other transcatheter re-intervention procedure (Transcatheter valve-in-valve procedure). (n=717) Intervention 2: Surgical valve replacement with biological or mechanical valve - Surgical valve replacement with biological or mechanical valve - standard surgery. Redo surgical aortic valve replacement performed. No further details reported (type of valve or invasiveness of surgery). Duration NA - surgical intervention. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Type of transcatheter intervention: Not applicable
Funding	Other (Some authors have received honoraria from or served as a consultant for industry.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSCATHETER INTERVENTION (TRANSCATHETER VALVE-IN-VALVE) versus SURGICAL VALVE REPLACEMENT	

Protocol outcome 1: All-cause mortality at Latest reported time-point
- Actual outcome for Aortic valve: All-cause mortality at Mean (SD) 794 (675) days; Group 1: 170/717, Group 2: 147/717
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Comparable for large number of parameters reported, including age and surgical risk pre-specified in protocol. Others in protocol not reported (life expectancy, NYHA class, urgent indication and ejection fraction); Key confounders: Age (excluded if not accounted for); surgical risk; life expectancy; NYHA class; urgent indication; ejection fraction; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Cardiac mortality at Latest reported time-point
- Actual outcome for Aortic valve: Cardiovascular mortality at Mean (SD) 794 (675) days; Group 1: 82/717, Group 2: 78/717
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Comparable for large number of parameters reported, including age and surgical risk pre-specified in protocol. Others in protocol not reported (life expectancy, NYHA class, urgent indication and ejection fraction); Key confounders: Age (excluded if not accounted for); surgical risk; life expectancy; NYHA class; urgent indication; ejection fraction; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Intervention-related mortality at 30 days
- Actual outcome for Aortic valve: All-cause mortality at 30 days; Group 1: 26/717, Group 2: 52/717; Comments: OR (95% CI) of 0.48 (0.30-0.78) reported in study.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Comparable for large number of parameters reported, including age and surgical risk pre-specified in protocol. Others in protocol not reported (life expectancy, NYHA class, urgent indication and ejection fraction); Key confounders: Age (excluded if not accounted for); surgical risk; life expectancy; NYHA class; urgent indication; ejection fraction; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Onset or exacerbation of heart failure at Latest reported time-point
- Actual outcome for Aortic valve: Hospitalisation for heart failure at Mean (SD) 794 (675) days; Group 1: 199/717, Group 2: 144/717
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Comparable for large number of parameters reported, including age and surgical risk pre-specified in protocol. Others in protocol not reported (life expectancy, NYHA class, urgent indication and ejection fraction); Key confounders: Age (excluded if not accounted for); surgical risk; life expectancy; NYHA class; urgent indication; ejection fraction; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 5: Intervention-related stroke or TIA at 30 days
- Actual outcome for Aortic valve: All-cause stroke at 30 days; Group 1: 7/717, Group 2: 3/717; Comments: OR (95% CI) of 2.35 (0.60-9.11) reported in study.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Comparable for large number of parameters reported, including age and surgical risk pre-specified in protocol. Others in protocol not reported (life expectancy, NYHA class, urgent indication and ejection fraction); Key confounders: Age (excluded if not accounted for); surgical risk; life expectancy; NYHA class; urgent indication; ejection fraction; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 6: Intervention-related major bleeding at 30 days

- Actual outcome for Aortic valve: Major or life-threatening bleeding at 30 days; Group 1: 29/717, Group 2: 34/717; Comments: OR (95% CI) of 0.85 (0.51-1.41) reported in study. Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Comparable for large number of parameters reported, including age and surgical risk pre-specified in protocol. Others in protocol not reported (life expectancy, NYHA class, urgent indication and ejection fraction); Key confounders: Age (excluded if not accounted for); surgical risk; life expectancy; NYHA class; urgent indication; ejection fraction; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life at Latest reported time-point; Need for re-intervention at Latest reported time-point; Length of stay (following initial intervention) at Post-intervention; Re-hospitalisation at <12 months postoperatively; Re-hospitalisation at ≥12 months postoperatively; Intervention-related major vascular complications (defined as those requiring intervention for a vascular complication) at 30 days

Study	**Ejiofor 2016[6]**
Study type	Retrospective cohort study
Number of studies (number of participants)	1 (n=44)
Countries and setting	Conducted in USA; Setting: Secondary care - hospital
Line of therapy	2nd line intervention
Duration of study	Intervention + follow up: Up to 3 years
Method of assessment of guideline condition	Unclear method of assessment/diagnosis: Identified retrospectively from database. Eligibility determined by multidisciplinary heart team.
Stratum	Aortic valve: Patients undergoing reoperative aortic valve operations
Subgroup analysis within study	Not applicable
Inclusion criteria	>17 years of age; underwent reoperative aortic valve operation for biological valves between January 2002 and May 2015
Exclusion criteria	Patients with prior mechanical prostheses or homografts; active endocarditis; those that had any concomitant coronary, valvular or aortic interventions
Recruitment/selection of patients	All those matching inclusion criteria between January 2002 and May 2015. For analysis, only a matched group of 44 patients (n=22 in each arm) were included. Matching was performed based on STS PROM score.
Age, gender and ethnicity	Age - Mean (SD): TAVI, 75.0 (9.6) years; redo SAVR, 74.5 (10.4) years - n=44. Gender (M:F): TAVI, 14/8; redo SAVR, 13/9 - n=44. Ethnicity: Not reported

Further population details	1. Age: Age ≥75 years (In the 44 matched patients included in analysis, mean age was ~75 years in both arms).
Extra comments	. Note: all variables are reported for the cohort after matching was performed, in n=44 patients. Renal failure, 27.3% vs. 18.2%; hypertension, 95.5% vs. 90.9%; cerebrovascular disease, 13.6% vs. 18.2%; history of cerebrovascular accident, 22.7% vs. 13.6%; peripheral vascular disease, 27.3% vs. 22.7%; NYHA class III/IV, 95.5% vs. 72.7%; previous coronary artery bypass grafting, 63.6% vs. 54.4%; median (IQR) ejection fraction, 55.0 (35.0-60.0)% vs. 55.0 (50.0-60.0)%; mean (SD) preoperative aortic valve gradient, 39.8 (13.6) mmHg vs. 46.6 (26.5) mmHg; mean (SD) STS PROM score, 7.54 (3.0) vs. 7.70 (3.0); median (IQR) years since previous surgery, 9.0 (5.0-15.0) years vs. 9.5 (4.0-12.0) years.
Indirectness of population	No indirectness
Interventions	(n=22) Intervention 1: Transcatheter intervention (including TAVI-in-TAVI). Transcatheter aortic valve-in-valve replacement for failed bioprosthetic surgical valves. Eligibility for the procedure was determined by multidisciplinary heart team. Risk assessment consisted of independent patient evaluation by two cardiac surgeons. Transcatheter procedures planned using computed tomography. First option was transfemoral approach, with transaortic, transapical and subclavian approaches alternatives if iliofemoral vessels not adequate. Edwards Sapien, Sapien XT or Medtronic CoreValve used. Duration NA. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Type of transcatheter intervention: Other transcatheter re-intervention procedure (Does not appear to be TAVI-in-TAVI as no mention of prior TAVI being performed. Original bioprosthetic valves likely to have been inserted via surgery in all patients.). (n=22) Intervention 2: Surgical valve replacement with biological or mechanical valve. Surgical aortic valve replacement for failed bioprosthetic surgical valves. Eligibility for the procedure was determined by multidisciplinary heart team.

	Risk assessment consisted of independent patient evaluation by two cardiac surgeons. Preoperative chest radiography and computed tomography scans, with and without contrast, were performed. Minimally invasive access through upper hemisternotomy performed where feasible, and full sternotomy in cases where it was not (31.8% by full sternotomy and 68.2% by upper hemisternotomy). Patients received biological (81.8%; Carpentier-Edwards Magna/Pericardial or Sorin Mitroflow) or mechanical valves (18.2%; St. Jude). Duration NA. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Type of transcatheter intervention: Not applicable
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSCATHETER INTERVENTION (TRANSCATHETER VALVE-IN-VALVE) versus SURGICAL VALVE REPLACEMENT WITH BIOLOGICAL OR MECHANICAL VALVE - STANDARD OR MINIMALLY INVASIVE

Protocol outcome 1: All-cause mortality at Latest reported time-point
- Actual outcome for Aortic valve: All-cause mortality (KM estimates of survival given for each group) at 3 years; data for this outcome was not extracted as there appeared to be inconsistencies between results reported in the text of the study and the data that was presented in the survival curve, meaning it was difficult to know which results were correct. No event rates at 3 years were reported, only the KM estimates were presented.
Risk of bias: All domain - ; Indirectness of outcome: No indirectness

Protocol outcome 2: Intervention-related mortality at 30 days
- Actual outcome for Aortic valve: Operative mortality at Unclear; Group 1: 0/22, Group 2: 1/22
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: Serious indirectness, Comments: unclear whether includes all events up to 30 days as time-point is unclear; Baseline details: Of the listed important confounders, there is a large difference in proportion with NYHA class III/IV symptoms. Some other pre-specified ones not reported.; Key confounders: age (excluded if not accounted for); surgical risk; life expectancy; NYHA class; urgent indication, ejection fraction; Blinding details: Retrospective review of data so not blinded at time data recorded.; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Intervention-related stroke or TIA at 30 days

- Actual outcome for Aortic valve: Postoperative permanent stroke at Postoperative; Group 1: 0/22, Group 2: 2/22
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: Serious indirectness, Comments: unclear whether includes all of those up to 30 days as time-point is unclear; Baseline details: Of the listed important confounders, there is a large difference in proportion with NYHA class III/IV symptoms. Some other pre-specified ones not reported.; Key confounders: age (excluded if not accounted for); surgical risk; life expectancy; NYHA class; urgent indication, ejection fraction; Blinding details: Retrospective review of data so not blinded at time data recorded.; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Need for re-intervention at Latest reported time-point
- Actual outcome for Aortic valve: Reintervention due to paravalvular leakage at Unclear; Group 1: 0/22, Group 2: 0/22; Comments: Reporting of this outcome is unclear, as only mentions that of those with mild paravalvular leakage, none required reintervention. No information as to whether any reoperations performed for other reasons or time-point this data covers.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: Serious indirectness, Comments: Time-point unclear, may be immediate postoperative period or during 3 year follow-up. Also no information as to whether any reoperations performed for other reasons.; Baseline details: Of the listed important confounders, there is a large difference in proportion with NYHA class III/IV symptoms. Some other pre-specified ones not reported.; Key confounders: age (excluded if not accounted for); surgical risk; life expectancy; NYHA class; urgent indication, ejection fraction; Blinding details: Retrospective review of data so not blinded at time data recorded.; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 5: Length of stay (following initial intervention) at Post-intervention
- Actual outcome for Aortic valve: Intensive care length of stay at Postoperative; Group 1: mean 0 hours (SD 0); n=22, Group 2: mean 0 hours (SD 0); n=22; Comments: Results reported only as median (interquartile range): transcatheter, 0 (0-50) hours; surgical, 68 (43-98) hours
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Of the listed important confounders, there is a large difference in proportion with NYHA class III/IV symptoms. Some other pre-specified ones not reported.; Key confounders: age (excluded if not accounted for); surgical risk; life expectancy; NYHA class; urgent indication, ejection fraction; Blinding details: Retrospective review of data so not blinded at time data recorded.; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for Aortic valve: Hospital length of stay at Postoperative; Group 1: mean 0 Days (SD 0); n=22, Group 2: mean 0 Days (SD 0); n=22; Comments: Results reported only as median (interquartile range): transcatheter, 5 (2-7) days; surgical, 10.5 (8-18) days
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Of the listed important confounders, there is a large difference in proportion with NYHA class III/IV symptoms. Some other pre-specified ones not reported.; Key confounders: age (excluded if not accounted for); surgical risk; life expectancy; NYHA class; urgent indication, ejection fraction; Blinding details: Retrospective review of data so not blinded at time data recorded.; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 6: Re-hospitalisation at <12 months postoperatively - Actual outcome for Aortic valve: Readmission at 30 days; Group 1: 5/22, Group 2: 3/22 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Definition: no explanation as to whether general hospital readmission or readmission due to valve problems; Indirectness of outcome: No indirectness ; Baseline details: Of the listed important confounders, there is a large difference in proportion with NYHA class III/IV symptoms. Some other pre-specified ones not reported.; Key confounders: age (excluded if not accounted for); surgical risk; life expectancy; NYHA class; urgent indication, ejection fraction; Blinding details: Retrospective review of data so not blinded at time data recorded.; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Cardiac mortality at Latest reported time-point; Quality of life at Latest reported time-point; Onset or exacerbation of heart failure at Latest reported time-point; Intervention-related major bleeding at 30 days; Re-hospitalisation at ≥12 months postoperatively; Intervention-related major vascular complications (defined as those requiring intervention for a vascular complication) at 30 days

Study	**Malik 2020[35]**
Study type	Retrospective cohort study
Number of studies (number of participants)	1 (n=1420)
Countries and setting	Conducted in USA; Setting: Secondary care - hospitals of different centres
Line of therapy	2nd line intervention
Duration of study	Intervention time: Limited to in-hospital outcomes
Method of assessment of guideline condition	Method of assessment /diagnosis not stated: Patients identified by codes from a database
Stratum	Aortic valve: Those undergoing aortic valve reoperation by TAVI valve-in-valve or redo surgical aortic valve replacement
Subgroup analysis within study	Not applicable:
Inclusion criteria	Previously received prosthetic valve and undergoing subsequent TAVI valve-in-valve or redo surgical aortic valve replacement procedure
Exclusion criteria	Hospitalisation with concomitant diagnoses of other valve disease (mitral, pulmonary and tricuspid) or other congenital rheumatic valve disease; hospitalisation with diagnosis of endocarditis; missing data for age, sex, length of stay or death
Recruitment/selection of patients	Those matching criteria between 2012 and 2016 in National Inpatient Sample database. Retrospective review.

Age, gender and ethnicity	Age - Mean (SD): TAVI, 73.7 (10.4) years; SAVR, 73.3 (8.6) years. Gender (M:F): TAVI, 375/335; SAVR, 390/320. Ethnicity: White: TAVI, 78.2% and SAVR, 81.7%; black: TAVI, 2.8% and SAVR, 4.9%; other: TAVI, 10.6% and SAVR, 9.2%; missing: TAVI, 6.3% and SAVR, 6.3%.
Further population details	1. Age: Age <75 years (After matching, mean age was <75 years in both arms).
Extra comments	People with failed bioprosthetic valves. Hypertension, 83.1% vs. 78.2%; heart failure, 66.9% vs. 64.1%; atrial fibrillation, 52.8% vs. 48.6%; arrhythmias, 69.7% vs. 64.8%; chronic pulmonary disease, 36.6% vs. 39.4%; peripheral vascular disease, 26.8% vs. 21.8%; neurological disorders, 6.3% vs. 7.7%; chronic kidney disease, 26.8% vs. 26.8%; history of myocardial infarction, 12.0% vs. 12.0%; liver disease, 4.2% vs. 4.9%
Indirectness of population	No indirectness
Interventions	(n=710) Intervention 1: Transcatheter intervention (including TAVI-in-TAVI). Transcatheter valve-in-valve procedure. No information on type of valve used or any further details of the procedure. Duration NA. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Type of transcatheter intervention: Other transcatheter re-intervention procedure (Reported to be TAVI valve-in-valve, with surgical biological valves being the initial valve used.). (n=710) Intervention 2: Surgical valve replacement with biological or mechanical valve. Redo surgical aortic valve replacement performed for failed bioprosthetic valve. No information on the invasiveness of the surgery performed or the type of valve used (biological or mechanical). Duration NA. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Type of transcatheter intervention: Not applicable
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSCATHETER INTERVENTION (VALVE-IN-VALVE) versus SURGICAL VALVE REPLACEMENT WITH BIOLOGICAL OR MECHANICAL VALVE - INVASIVENESS OF SURGERY AND TYPE OF VALVE UNCLEAR

Protocol outcome 1: Intervention-related mortality at 30 days
- Actual outcome for Aortic valve: In-hospital mortality at In-hospital; OR; 0.14 (95%CI 0.02 to 1.13) (P-value: 0.064) , Comments: Also reports the proportion with events as follows: TAVI, <1%; SAVR, 4.9%. The odds ratio reported has wider confidence intervals than those calculated using the number of events reported but it is unclear from the report how this was calculated;
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: Serious indirectness, Comments: Limited to in-hospital and does not necessarily cover 30 day time period in all patients; Baseline details: Though age is matched, none of other important confounders listed in protocol are reported so unclear if matched; Key confounders: age; surgical risk; life expectancy; NYHA class; urgent indication; ejection fraction; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Intervention-related major bleeding at 30 days
- Actual outcome for Aortic valve: Postoperative haemorrhage at In-hospital; Group 1: 125/710, Group 2: 220/710; Comments: Calculated from percentages reported in the paper. Odds ratio also reported in the paper: 0.48 (0.29-0.79), P-value 0.005. The odds ratio reported has wider confidence intervals than those calculated using the number of events reported but it is unclear from the report how this was calculated. This outcome was analysed rather than the transfusion outcome as it is more general and may include additional major bleeding events that did not require transfusion, for example those that required reoperation instead. Note many of these may also be included in the transfusion outcome.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: Serious indirectness, Comments: Limited to in-hospital and does not necessarily cover 30 day time period in all patients, also unclear whether all were major events; Baseline details: Though age is matched, none of other important confounders listed in protocol are reported so unclear if matched; Key confounders: age; surgical risk; life expectancy; NYHA class; urgent indication; ejection fraction; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for Aortic valve: Transfusion at In-hospital; Group 1: 85/710, Group 2: 220/710; Comments: Calculated from percentages reported in the paper. Paper also reports odds ratio: 0.30 (0.17-0.54), P-value <0.001. This outcome was not included in the analysis as postoperative haemorrhage is more general and may have included additional major bleeding events not captured under the transfusion outcome. Additionally, transfusion may have been performed for reasons other than major bleeding. Note many of these may also be included in the postoperative haemorrhage outcome.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: Serious indirectness, Comments: Limited to in-hospital and does not necessarily cover 30 day time period in all patients; Baseline details: Though age is matched, none of other important confounders listed in protocol are reported so unclear if matched; Key confounders: age; surgical risk; life expectancy; NYHA class; urgent indication; ejection fraction; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Length of stay (following initial intervention) at Post-intervention
- Actual outcome for Aortic valve: Length of hospital stay at In-hospital; Group 1: mean 6.6 days (SD 0); n=710, Group 2: mean 9.6 days (SD 0); n=710;

Comments: Standard deviation not reported so cannot be analysed. P<0.01.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Outcome reporting: does not provided standard deviation so cannot be analysed; Indirectness of outcome: No indirectness; Baseline details: Though age is matched, none of other important confounders listed in protocol are reported so unclear if matched; Key confounders: age; surgical risk; life expectancy; NYHA class; urgent indication; ejection fraction; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Intervention-related major vascular complications (defined as those requiring intervention for a vascular complication) at 30 days
- Actual outcome for Aortic valve: Vascular complications at In-hospital; Group 1: 8/710, Group 2: 15/710; Comments: Calculated from percentages reported in the paper. Also reports odds ratio: 0.49 (0.12-2.0), P-value 0.318. The odds ratio reported has wider confidence intervals than those calculated using the number of events reported but it is unclear from the report how this was calculated.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: Serious indirectness, Comments: Limited to in-hospital and does not necessarily cover 30 day time period in all patients. Also unclear whether all needed intervention.; Baseline details: Though age is matched, none of other important confounders listed in protocol are reported so unclear if matched; Key confounders: age; surgical risk; life expectancy; NYHA class; urgent indication; ejection fraction; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study	All-cause mortality at Latest reported time-point; Cardiac mortality at Latest reported time-point; Quality of life at Latest reported time-point; Onset or exacerbation of heart failure at Latest reported time-point; Intervention-related stroke or TIA at 30 days; Need for re-intervention at Latest reported time-point; Re-hospitalisation at <12 months postoperatively; Re-hospitalisation at ≥12 months postoperatively

Study	**Sedeek 2019[47]**
Study type	Retrospective cohort study
Number of studies (number of participants)	1 (n=350)
Countries and setting	Conducted in USA; Setting: Secondary care - hospital
Line of therapy	2nd line intervention
Duration of study	Intervention + follow up: Median (IQR) follow-up was 2.1 (1.2-4.2) years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Heart team evaluation performed
Stratum	Aortic valve: Those with failing surgical aortic bioprostheses undergoing TAVI valve-in-valve or redo surgical aortic valve replacement
Subgroup analysis within study	Not applicable:
Inclusion criteria	Failing stented aortic biological prostheses undergoing a repeat replacement intervention
Exclusion criteria	No exclusion criteria reported
Recruitment/selection of patients	Those matching criteria between November 2008 and May 2018
Age, gender and ethnicity	Age - Median (IQR): 74 (65-79). Gender (M:F): 250/100. Ethnicity: Not reported
Further population details	1. Age: Age <75 years (Median age for whole cohort was 74 years (IQR, 65-79), though the median was 79 years (76-83) in TAVI group and 72 years (63-77) in SAVR group.).

Extra comments	Previous operation was stented surgical bioprosthetic valve replacement. primary indication for operation: aortic stenosis, 40% vs. 43%; aortic regurgitation, 13% vs. 17%; aortic stenosis and regurgitation, 47% vs. 36%; other, 0% vs. 3%. All continuous variables below are reported as median (IQR). Ejection fraction, 0.56 (0.45-0.62)% vs. 0.62 (0.55-0.66)%; STS PROM, 7.5 (4.9-10.7)% vs. 3.0 (2.1-5.3)%; time to repeat operation, 9 (7-12) years vs. 7 (4-10) years; hypertension, 88% vs. 73%; dialysis, 1% vs. 3%; infectious endocarditis, 6% vs. 18%; severe chronic lung disease, 18% vs. 3%; peripheral vascular disease, 53% vs. 14%; cerebrovascular diseases, 33% vs. 18%; previous coronary artery bypass grafting, 48% vs. 29%; NYHA class III or IV, 83% vs. 62%; atrial fibrillation, 47% vs. 33%; ≥1 diseased coronary arteries, 64% vs. 47%; left coronary artery stenosis ≥50%, 14% vs. 9%; medical inotropic agents, 2% vs. 2%; aortic stenosis, 87% vs. 82%; moderate or severe aortic regurgitation, 60% vs. 53%; mitral stenosis, 10% vs. 13%; moderate or severe mitral regurgitation, 34% vs. 30%; moderate or severe tricuspid regurgitation, 32% vs. 25%; ≥3 cardiac operations, 22% vs. 10%; non-elective operative status, 28% vs. 23%; low STS PROM group, 8% vs. 49%; intermediate STS PROM group, 51% vs. 40%; high STS PROM group, 41% vs. 11%
Indirectness of population	No indirectness
Interventions	(n=90) Intervention 1: Transcatheter intervention (including TAVI-in-TAVI). TAVI valve-in-valve where bioprosthetic surgical valves were previously used for replacement. Arterial access was through femoral artery in 88% (n=79), left ventricular apex in 11% (n=10) and innominate artery in 1% (n=1). Valves used were Sapien S3 in 33% (n=30), Sapien XT in 31% (n=28), Sapien in 2% (n=2), Evolut in 28% (n=25) and CoreValve in 6% (n=5). Duration NA. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Type of transcatheter intervention: Other transcatheter re-intervention procedure (TAVI valve-in-valve. Previous operation was surgical with biological valves, so not TAVI-in-TAVI). (n=260) Intervention 2: Surgical valve replacement with biological or mechanical valve. Surgical aortic valve replacement of failing aortic biological valves that had been previously inserted by surgery in the majority of patients (note, one had a failing transcatheter valve). No information on the invasiveness of surgery. Type of valve used: stented bioprosthesis, 57%; mechanical prosthesis, 39%; and stentless bioprosthesis, 4%. Duration NA. Concurrent medication/care: Concomitant procedures were performed in 30% of patients (n=79): mitral valve operation, 20% (n=53); tricuspid valve operation, 12% (n=30); and other cardiac procedures, 21% (n=55). Indirectness: No indirectness

	Further details: 1. Type of transcatheter intervention: Not applicable
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSCATHETER INTERVENTION (TAVI VALVE-IN-VALVE) versus SURGICAL VALVE REPLACEMENT WITH BIOLOGICAL OR MECHANICAL VALVE - UNCLEAR INVASIVENESS OF SURGERY

Protocol outcome 1: All-cause mortality at Latest reported time-point
- Actual outcome for Aortic valve: Mortality at Median (IQR) follow-up reported: 2.1 (1.2-4.2) years; Group 1: Observed events 19 n=90 ; Group 2: Observed events 49 n=260; HR 1.18; Lower CI 0.62 to Upper CI 2.22; Test statistic: P-value: 0.612; Follow up details: Median follow-up 2.1 (1.2-4.2) years. Median follow-up was 1.6 (1.1-3.0) years in TAVI group and 2.3 (1.2-4.5) years in SAVR group.; Comments: Multivariate analysis that has adjusted for age, STS PROM score and internal aortic prosthesis diameter
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 - Comparability of care: patients in the SAVR group have concomitant procedures described, and no concomitant procedures mentioned for TAVI so this is a difference that has not been accounted for in analysis; Indirectness of outcome: No indirectness, Comments: Though other outcomes were reported, only the mortality outcome was extracted as data that had been adjusted for age (key confounder) has been reported only for this outcome. Other outcomes in the study are at an even higher risk of confounding bias and therefore were not extracted, as pre-specified in the protocol.; Baseline details: Baseline variables differed as the population was not matched, but adjustment for age and other variables was performed for this outcome. Of the key or important confounders listed in the protocol, age and surgical risk (STS PROM score) were adjusted for in the analysis.; Key confounders: age; surgical risk; life expectancy; NYHA class; urgent indication; ejection fraction; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Cardiac mortality at Latest reported time-point; Intervention-related mortality at 30 days; Quality of life at Latest reported time-point; Onset or exacerbation of heart failure at Latest reported time-point; Intervention-related stroke or TIA at 30 days; Intervention-related major bleeding at 30 days; Need for re-intervention at Latest reported time-point; Length of stay (following initial intervention) at Post-intervention; Re-hospitalisation at <12 months postoperatively; Re-hospitalisation at ≥12 months postoperatively; Intervention-related major vascular complications (defined as those requiring intervention for a vascular complication) at 30 days

Study	**Silaschi 2017[49]**
Study type	Retrospective cohort study
Number of studies (number of participants)	1 (n=130)
Countries and setting	Conducted in Germany, United Kingdom; Setting: Secondary care - two different hospitals
Line of therapy	2nd line intervention
Duration of study	Intervention + follow up: Median follow-up was 675 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Assessment for type of procedure to perform done by heart team
Stratum	Aortic valve: Those undergoing TAVI valve-in-valve or redo surgical aortic valve replacement for failing surgical aortic bioprostheses
Subgroup analysis within study	Not applicable
Inclusion criteria	Failing aortic bioprothesis undergoing TAVI valve-in-valve procedure or redo surgical aortic valve replacement
Exclusion criteria	Not reported
Recruitment/selection of patients	Those matching criteria between 2008 and 2015 for TAVI valve-in-valve procedure and between 2002 and 2015 for redo surgical aortic valve replacement at two different hospitals
Age, gender and ethnicity	Age - Mean (SD): TAVI, 78.6 (7.5) years; SAVR, 72.9 (6.6) years. Gender (M:F): TAVI, 41/30; SAVR, 36/23. Ethnicity: Not reported
Further population details	1. Age: Age ≥75 years (Mean age of whole cohort >75 years - >75 years in TAVI valve-in-valve group and <75 years in redo SAVR group).

Extra comments	Prior replacement operation performed by surgery using bioprosthetic valves. Previous valve type: stented, 85.9% vs. 79.7%; stentless, 12.7% vs. 15.3%; unknown, 2.8% vs. 1.7%. Previous procedure performed: SAVR, 63% vs. 78%; SAVR + CABG, 32.4% vs. 16.9%; SAVR + other, 5.6% vs. 5.1%. Mode of deterioration: stenosis, 45.1% vs. 40.7%; regurgitation, 38.0% vs. 35.6%; mixed, 16.9% vs. 22%; unknown, 0% vs. 1.7%. Continuous variables below are mean (SD). Logistic EuroSCORE I, 25.1 (18.9)% vs. 16.8 (9.3)%; peripheral vascular disease, 32.5% vs. 13.6%; previous stroke/TIA, 14.1% vs. 10.2%: LVEF 30-50%, 7% vs. 22%; LVEF <30%, 8.5% vs. 5.1%; >1 prior cardiac operation, 8.5% vs. 3.4%; time since valve replacement, 9.9 (4.9) years vs. 9.1 (5.6) years; gradient, 33.0 (17.8) mmHg vs. 37.3 (13.7) mmHg; pre-existent patient prosthesis mismatch, 5.6% vs. 8.5%
Indirectness of population	No indirectness
Interventions	(n=71) Intervention 1: Transcatheter intervention (including TAVI-in-TAVI). Transcatheter valve-in-valve procedure for failing bioprosthetic valves that had been inserted originally through surgical replacement operation. Edwards Sapien valves used in 50.7% (n=36), CoreValve used in 39.5% (n=28), St. Jude Portico valve used in 4.2% (n=3), Medtronic Engager valve used in 2.8% (n=2) and JenaValve used in 2.8% (n=2). Access was transapical in 46.5% (n=33), transvascular in 49.3 (n=35) and transaortic in 4.2% (n=3). Duration NA. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Type of transcatheter intervention: Other transcatheter re-intervention procedure (TAVI valve-in-valve performed for valves that were previously surgically implanted, not TAVI-in-TAVI). (n=59) Intervention 2: Surgical valve replacement with biological or mechanical. Redo surgical aortic valve replacement for bioprosthetic valves that had previously been implanted by surgery. Bioprostheses were used for the redo replacement in all patients, which were stented in 94.9% (n=56) and stentless in 5.1% (n=3). Invasiveness of surgery unclear. Duration NA. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Type of transcatheter intervention: Not applicable
Funding	Other (Research post of first author funded through King's College Hospital Charity, London, UK)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSCATHETER INTERVENTION (TAVI VALVE-IN-VALVE) versus SURGICAL VALVE

REPLACEMENT WITH BIOLOGICAL OR MECHANICAL VALVE - BIOLOGICAL VALVES AND UNCLEAR INVASIVENESS OF SURGERY

Protocol outcome 1: All-cause mortality at Latest reported time-point
- Actual outcome for Aortic valve: All-cause mortality at 180 days; Group 1: 5/46, Group 2: 4/51; Comments: TAVI: deaths due to accidental tearing of bypass graft during transaortic access leading to myocardial infarction and right heart failure (n=1), failure to recover from pre-operative low cardiac output after uneventful TAVI procedure (n=1), respiratory failure due to severe pulmonary emphysema (n=1), acute heart failure (n=1) and fatal transcatheter heart valve endocarditis (n=1); SAVR: deaths due to injury or aorta and right ventricle during sternotomy which was not successfully repaired (n=1), sudden heart block (n=1) or myocardial infarction (n=1) due to left main obstruction caused by misplacement of the bioprosthetic valve and unknown cause (n=1). Note this include those deaths reported under procedural and 30-day mortality outcomes.
Able to extract results as a HR by using the survival curve up to 1 year, therefore HR used in analysis and not dichotomous results.
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - High, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Though age was a factor considered for matching when selecting the SAVR group, there remains a larger difference in age between the groups compared to similar included studies. Therefore, the study has been included but downgraded further for risk of bias on this basis. Outcome reporting: reports at 180 days, whereas there is sufficient data in the survival curve to suggest 1 year time-point data could have been reported - 2 extra deaths in the TAVI group between 180 days and 365 days.; Indirectness of outcome: No indirectness ; Baseline details: Only simple matching performed to select SAVR group, based on age and procedure. Despite matching for age (key confounder), it is >75 years in TAVI and <75 years in SAVR. Surgical risk and ejection fraction also different, other confounders in protocol not mentioned.; Key confounders: age; surgical risk; life expectancy; NYHA class; urgent indication; ejection fraction; Group 1 Number missing: 25, Reason: Not reported.; Group 2 Number missing: 8, Reason: Not reported.
- Actual outcome for Aortic valve: All-cause mortality at 1 year; Group 1: Observed events 7 n=71 ; Group 2: Observed events 4 n=59; HR 1.35; Lower CI 0.39 to Upper CI 4.68; Log rank variance: 2.48; Log rank observed minus expected events: 0.74; Advantage to research or control? C; Actuarial or Kaplan Meier curves reported? Yes; Follow up details: Median follow-up 675 days; Comments: This was extracted using the curve provided, reading the number of deaths and those censored (upward flicks on graph). Note, the graph suggests that the number analysed at 180 days as reported in the table may be incorrect.
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - High, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Though age was a factor considered for matching when selecting the SAVR group, there remains a larger difference in age between the groups compared to similar included studies. Therefore, the study has been included but downgraded further for risk of bias on this basis. Outcome reporting: median follow-up was 675 days, so possible could have reported data at longer than 1-year on the survival curve.; Indirectness of outcome: No indirectness ; Baseline details: Only simple matching performed to select SAVR group, based on age and procedure. Despite matching for age (key confounder), it is >75 years in TAVI and <75 years in SAVR. Surgical risk and ejection fraction also different, other confounders in protocol not mentioned.; Key confounders: age; surgical risk; life expectancy; NYHA class; urgent indication; ejection fraction; Group 1 Number missing: 25, Reason: Not reported.; Group 2 Number missing: 8, Reason: Not reported.

Protocol outcome 2: Cardiac mortality at Latest reported time-point

- Actual outcome for Aortic valve: Cardiovascular mortality. Defined as used in VARC-2 guidance. at 30 days; Group 1: 2/71, Group 2: 3/59
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Though age was a factor considered for matching when selecting the SAVR group, there remains a larger difference in age between the groups compared to similar included studies. Therefore, the study has been included but downgraded further for risk of bias on this basis.; Indirectness of outcome: Serious indirectness, Comments: Indirectness as reported at time-point that is <3 months and interested in long term data for this outcome ideally; Baseline details: Only simple matching performed to select SAVR group, based on age and procedure. Despite matching for age (key confounder), it is >75 years in TAVI and <75 years in SAVR. Surgical risk and ejection fraction also different, other confounders in protocol not mentioned.; Key confounders: age; surgical risk; life expectancy; NYHA class; urgent indication; ejection fraction; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Intervention-related mortality at 30 days
- Actual outcome for Aortic valve: Intervention-related mortality at 30 days; Group 1: 1/71, Group 2: 3/59; Comments: This was not reported as an outcome within the study, but the reason for each of the 6 deaths within 30 days were given. The following were included as intervention-related: TAVI, accidental tearing of bypass graft during transaortic access leading to myocardial infarction and right heart failure (n=1); redo SAVR, injury or aorta and right ventricle during sternotomy which was not successfully repaired (n=1) and sudden heart block (n=1) or myocardial infarction (n=1) due to left main obstruction caused by misplacement of the bioprosthetic valve.
An additional 2 deaths were reported in the TAVI group within 30 days, but were not felt to be intervention-related based on the reason provided in the paper: failure to recover from pre-operative low
cardiac output after uneventful TAVI procedure (n=1) and respiratory failure due to severe pulmonary emphysema (n=1).
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Though age was a factor considered for matching when selecting the SAVR group, there remains a larger difference in age between the groups compared to similar included studies. Therefore, the study has been included but downgraded further for risk of bias on this basis.; Indirectness of outcome: No indirectness ; Baseline details: Only simple matching performed to select SAVR group, based on age and procedure. Despite matching for age (key confounder), it is >75 years in TAVI and <75 years in SAVR. Surgical risk and ejection fraction also different, other confounders in protocol not mentioned.; Key confounders: age; surgical risk; life expectancy; NYHA class; urgent indication; ejection fraction; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Intervention-related stroke or TIA at 30 days
- Actual outcome for Aortic valve: Non-disabling or disabling stroke. Defined according to VARC-2 criteria. at 30 days; Group 1: 0/71, Group 2: 2/59; Comments: Note that both of the events in the surgery group were classed as disabling stroke events. No non-disabling strokes were reported for either group.
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Though age was a factor considered for matching when selecting the SAVR group, there

remains a larger difference in age between the groups compared to similar included studies. Therefore, the study has been included but downgraded further for risk of bias on this basis.; Indirectness of outcome: No indirectness ; Baseline details: Only simple matching performed to select SAVR group, based on age and procedure. Despite matching for age (key confounder), it is >75 years in TAVI and <75 years in SAVR. Surgical risk and ejection fraction also different, other confounders in protocol not mentioned.; Key confounders: age; surgical risk; life expectancy; NYHA class; urgent indication; ejection fraction; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 5: Intervention-related major bleeding at 30 days
- Actual outcome for Aortic valve: Life-threatening or disabling bleeding. Defined according to VARC-2 criteria. at 30 days; Group 1: 7/71, Group 2: 20/59; Comments: This outcome was made up of the following criteria: transfusion of ≥4 units packed red blood cells, n=5 in TAVI and n=11 in SAVR; and reoperation for bleeding, n=2 in TAVI and n=9 in SAVR.
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Though age was a factor considered for matching when selecting the SAVR group, there remains a larger difference in age between the groups compared to similar included studies. Therefore, the study has been included but downgraded further for risk of bias on this basis.; Indirectness of outcome: No indirectness ; Baseline details: Only simple matching performed to select SAVR group, based on age and procedure. Despite matching for age (key confounder), it is >75 years in TAVI and <75 years in SAVR. Surgical risk and ejection fraction also different, other confounders in protocol not mentioned.; Key confounders: age; surgical risk; life expectancy; NYHA class; urgent indication; ejection fraction; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 6: Length of stay (following initial intervention) at Post-intervention
- Actual outcome for Aortic valve: Intensive care unit length of stay at Postoperative; Group 1: mean 2 days (SD 1.8); n=71, Group 2: mean 3.4 days (SD 2.9); n=59; Comments: P-value: 1.0
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Though age was a factor considered for matching when selecting the SAVR group, there remains a larger difference in age between the groups compared to similar included studies. Therefore, the study has been included but downgraded further for risk of bias on this basis; Indirectness of outcome: No indirectness ; Baseline details: Only simple matching performed to select SAVR group, based on age and procedure. Despite matching for age (key confounder), it is >75 years in TAVI and <75 years in SAVR. Surgical risk and ejection fraction also different, other confounders in protocol not mentioned.; Key confounders: age; surgical risk; life expectancy; NYHA class; urgent indication; ejection fraction; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 7: Re-hospitalisation at <12 months postoperatively
- Actual outcome for Aortic valve: Re-hospitalisation at 180 days; Group 1: 4/46, Group 2: 2/51
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Though age was a factor considered for matching when selecting the SAVR group,

there remains a larger difference in age between the groups compared to similar included studies. Therefore, the study has been included but downgraded further for risk of bias on this basis.; Indirectness of outcome: No indirectness ; Baseline details: Only simple matching performed to select SAVR group, based on age and procedure. Despite matching for age (key confounder), it is >75 years in TAVI and <75 years in SAVR. Surgical risk and ejection fraction also different, other confounders in protocol not mentioned.; Key confounders: age; surgical risk; life expectancy; NYHA class; urgent indication; ejection fraction; Group 1 Number missing: 25, Reason: Not reported.; Group 2 Number missing: 8, Reason: Not reported. Protocol outcome 8: Intervention-related major vascular complications (defined as those requiring intervention for a vascular complication) at 30 days - Actual outcome for Aortic valve: Major vascular complications - as defined by VARC-2 criteria. at 30 days; Group 1: 9/71, Group 2: 3/59 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Though age was a factor considered for matching when selecting the SAVR group, there remains a larger difference in age between the groups compared to similar included studies. Therefore, the study has been included but downgraded further for risk of bias on this basis.; Indirectness of outcome: No indirectness, Comments: May not all have had surgery but definition reasonable for major vascular complications; Baseline details: Only simple matching performed to select SAVR group, based on age and procedure. Despite matching for age (key confounder), it is >75 years in TAVI and <75 years in SAVR. Surgical risk and ejection fraction also different, other confounders in protocol not mentioned.; Key confounders: age; surgical risk; life expectancy; NYHA class; urgent indication; ejection fraction; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life at Latest reported time-point; Onset or exacerbation of heart failure at Latest reported time-point; Need for re-intervention at Latest reported time-point; Re-hospitalisation at ≥12 months postoperatively

Study	**Spaziano 2017[51]**
Study type	Retrospective cohort study
Number of studies (number of participants)	1 (n=156)
Countries and setting	Conducted in Belgium, Canada, Denmark, France, Germany, Italy; Setting: Secondary/tertiary care - 7 different hospitals/heart centres
Line of therapy	2nd line intervention
Duration of study	Intervention + follow up: Follow-up up to 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Heart team made decision about which intervention to perform
Stratum	Aortic valve: Those undergoing TAVI-in-SAVR or redo-SAVR for failing surgical bioprosthetic valves
Subgroup analysis within study	Not applicable
Inclusion criteria	Undergone TAVI-in-SAVR or redo-SAVR for failing surgical aortic bioprostheses (stenosis, regurgitation or both)
Exclusion criteria	Reason for redo-SAVR was paravalvular leak, valve endocarditis or valve thrombosis
Recruitment/selection of patients	Consecutive patients matching criteria at any of the centres between January 2007 and January 2015
Age, gender and ethnicity	Age - Mean (SD): TAVI, 78.0 (8.0) years; SAVR, 77.4 (5.0) years. Gender (M:F): TAVI, 39/39; SAVR, 44/34. Ethnicity: Not reported
Further population details	1. Age: Age ≥75 years (Mean age in both arms was >75 years).

Extra comments	Reason for failing bioprosthesis: aortic stenosis, 51% vs. 31%; aortic regurgitation, 22% vs. 50%; aortic stenosis and regurgitation, 27% vs. 19%. Continuous variables are reported as mean (SD). Logistic EuroSCORE, 22.1 (16.0) vs. 22.1 (18.3); STS score, 7.2 (4.9) vs. 5.8 (4.6); >1 prior cardiac surgery, 13% vs. 12%; NYHA class I, 1% vs. 1%; NYHA class II, 17% vs. 11%; NYHA class III, 55% vs. 45%; NYHA class IV, 27% vs. 43%; urgent procedure, 6% vs. 13%; LVEF, 50.7 (13.5)% vs. 49.5 (13.4)%; atrial flutter or fibrillation, 35% vs. 37%; hypertension, 72% vs. 73%; coronary artery disease requiring revascularisation, 42% vs. 32%; prior coronary artery bypass grafting, 31% vs. 23%; prior stroke, 9% vs. 12%; peripheral vascular disease, 14% vs. 17%; grade 1 chronic obstructive pulmonary disease, 9% vs. 3%; grade 2 chronic obstructive pulmonary disease, 12% vs. 8%; pulmonary hypertension, 31% vs. 36%; duration between redo procedure and initial replacement, 9.0 (4.3) years vs. 8.2 (5.1) years;
Indirectness of population	No indirectness
Interventions	(n=78) Intervention 1: Transcatheter intervention (including TAVI-in-TAVI). TAVI valve-in-valve for those with failing surgical aortic bioprosthetic valves (termed TAVI-in-SAVR). Transcatheter valves used were CoreValve in 59% (n=46) and Edwards valves (Sapien, Sapien XT or Sapien 3) in 41% (n=32). Access route was transfemoral in 54% (n=42), transapical in 31% (n=24) and other in 15% (n=12). Conversion to open heart surgery did not occur in any patients and a second transcatheter valve was required in 5.1% (n=4) of patients. Duration NA. Concurrent medication/care: N=33 (42%) had coronary artery disease that required revascularisation. Percutaneous coronary intervention was performed prior to TAVI-in-SAVR in n=32 patients and during the TAVI-in-SAVR procedure in n=1 patient. Indirectness: No indirectness Further details: 1. Type of transcatheter intervention: Other transcatheter re-intervention procedure (TAVI valve-in-valve performed for previous bioprosthetic surgical valves, termed TAVI-in-SAVR so is not TAVI-in-TAVI). (n=78) Intervention 2: Surgical valve replacement with biological or mechanical valve. Redo surgical aortic valve replacement for previous surgical bioprosthetic valves. Bioprosthetic valves were used in all cases for the redo operation. These were stented in 99% (n=77) and stentless in 1% (n=1). Invasiveness of surgery not clear. Duration NA. Concurrent medication/care: N=25 (32%) patients underwent either coronary artery bypass grafting (n=21) or percutaneous coronary intervention (n=4) concomitantly at the time or surgery due to coronary artery disease that required revascularisation. Indirectness: No indirectness

	Further details: 1. Type of transcatheter intervention: Not applicable
Funding	Funding not stated (No mention of funding but 14/20 listed authors reported to be proctor/consultant of one or more valve companies)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSCATHETER INTERVENTION (TAVI VALVE-IN-VALVE) versus SURGICAL VALVE REPLACEMENT WITH BIOLOGICAL OR MECHANICAL VALVE - BIOLOGICAL VALVES AND UNCLEAR INVASIVENESS

Protocol outcome 1: All-cause mortality at Latest reported time-point
- Actual outcome for Aortic valve: Mortality at 1 year; Group 1: Observed events 9 n=78 ; Group 2: Observed events 10 n=78; HR 0.89; Lower CI 0.36 to Upper CI 2.19; Log rank observed minus expected events: -0.55; Test statistic: Log-rank P-value: 0.80; Advantage to research or control? R; Actuarial or Kaplan Meier curves reported? Yes; Follow up details: Follow-up up to 1 year
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: After propensity-matching, comparable for many of the confounders listed in the protocol (age, surgical risk and LVEF), but still some differences for others (urgent indication and NYHA class); Key confounders: age; surgical risk; NYHA class; life expectancy; urgent indication; ejection fraction; Group 1 Number missing: 11; Group 2 Number missing: 4

Protocol outcome 2: Intervention-related mortality at 30 days
- Actual outcome for Aortic valve: Mortality at 30 days; Group 1: 3/78, Group 2: 5/78
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: After propensity-matching, comparable for many of the confounders listed in the protocol (age, surgical risk and LVEF), but still some differences for others (urgent indication and NYHA class); Key confounders: age; surgical risk; NYHA class; life expectancy; urgent indication; ejection fraction; Group 1 Number missing: 1; Group 2 Number missing: 0

Protocol outcome 3: Intervention-related stroke or TIA at 30 days
- Actual outcome for Aortic valve: Stroke - defined according to VARC-2 criteria at 30 days; Group 1: 1/78, Group 2: 0/78
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: After propensity-matching, comparable for many of the confounders listed in the protocol (age, surgical risk and LVEF), but still some differences for others (urgent indication and NYHA class); Key confounders: age; surgical risk; NYHA class; life expectancy; urgent indication; ejection fraction; Group 1 Number missing: 1; Group 2 Number missing: 0

Protocol outcome 4: Length of stay (following initial intervention) at Post-intervention - Actual outcome for Aortic valve: Total hospital length of stay at 30 days; Group 1: mean 0 days (SD 0); n=78, Group 2: mean 0 days (SD 0); n=78; Comments: Reported as median (IQR) rather than mean (SD), so cannot be analysed: TAVI, 9 (7-13) days; SAVR, 12 (8-24) days Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: After propensity-matching, comparable for many of the confounders listed in the protocol (age, surgical risk and LVEF), but still some differences for others (urgent indication and NYHA class); Key confounders: age; surgical risk; NYHA class; life expectancy; urgent indication; ejection fraction; Group 1 Number missing: 1; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Cardiac mortality at Latest reported time-point; Quality of life at Latest reported time-point; Onset or exacerbation of heart failure at Latest reported time-point; Intervention-related major bleeding at 30 days; Need for re-intervention at Latest reported time-point; Re-hospitalisation at <12 months postoperatively; Re-hospitalisation at ≥12 months postoperatively; Intervention-related major vascular complications (defined as those requiring intervention for a vascular complication) at 30 days

Study	Woitek 2020[60]
Study type	Retrospective cohort study
Number of studies (number of participants)	1 (n=258)
Countries and setting	Conducted in Germany; Setting: Secondary care
Line of therapy	2nd line
Duration of study	Intervention + follow up: Follow-up up to 12 months post-intervention
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Echocardiography performed and also CT
Stratum	Aortic valve: Those with degenerated aortic bioprosthesis undergoing redo TAVI or SAVR procedure. Surgery was initial operation.
Subgroup analysis within study	Not applicable
Inclusion criteria	Degenerated surgical aortic bioprosthesis; underwent redo procedure as TAVI or redo SAVR
Exclusion criteria	Patients that underwent redo SAVR as a TAVI procedure was not possible (e.g. degenerated mechanical valve, needed surgery other than mitral valve decalcification on other valves, or conditions not amenable to transcatheter treatment including infective endocarditis or paravalvular leaks as a separate indication of the procedure)
Recruitment/selection of patients	Retrospective review of database for those matching inclusion criteria between January 2006 and May 2017
Age, gender and ethnicity	Age - Mean (SD): TAVI, 76.2 (8.0 years); redo SAVR, 58.5 (14.4) years. Gender (M:F): TAVI, 92/55; redo SAVR, 66/45. Ethnicity: Not reported
Further population details	1. Age: Not stated / Unclear (Mean age differed between the groups, with one being <75 years and the other being >75 years. This was adjusted for the outcome reported.).

Extra comments	Body mass index, mean (SD): 28.4 (5.14) vs. 27.5 (4.43) kg/m²; STS-PROM score, mean (SD): 8.27 (6.12)% vs. 2.76 (2.09)%; NYHA class I (6.1% vs. 5.5%), II (21.1% vs. 39.1%), III (58.5% vs. 48.2%) and IV (14.3% vs. 7.3%); concomitant aortic surgery, 0% vs. 27.9%; concomitant mitral valve decalcification, 0% vs. 0.9%; concomitant Morrow procedure, 0% vs. 9.0%; concomitant aortocoronary bypass grafting, 0% vs. 12.6%; concomitant percutaneous coronary intervention, 2.1% vs. 0.9%; percutaneous coronary intervention within 30 days prior to procedure, 4.8% vs. 0%; medically treated coronary lesion, 4.1% vs. 2.7%; any coronary artery disease, 51.0% vs. 22.5%; aortocoronary bypass grafting >30 days prior, 32.7% vs. 9.9%; percutaneous coronary intervention >30 days prior, 12.2% vs. 6.3%; previous myocardial infarction, 8.8% vs. 6.3%; atrial fibrillation, 44.2% vs. 18.9%; chronic lung disease, 49.7% vs. 10.8%; cerebrovascular disease, 17.8% vs. 9.0%; peripheral arterial disease, 17.7% vs. 5.4%; diabetes, 36.1% vs. 16.2%; hypertension, 98.0% vs. 86.5%; history of endocarditis, 8.2% vs. 5.4%; glomerular filtration rate <45 ml/min/1.73 m², 25.2% vs. 7.2%; ejection fraction, mean (SD): 54.5 (13.9)% vs. 57.4 (10.2)%; aortic stenosis at baseline, 98% vs. 78.4%; severe aortic stenosis at baseline, 83.7% vs. 61.3%; aortic regurgitation at baseline, 75.5% vs. 76.6%; severe aortic regurgitation at baseline, 17.7% vs. 33.3%; mitral regurgitation at baseline, 91.8% vs. 73.9%; severe mitral regurgitation at baseline, 1.4% vs. 0%; tricuspid regurgitation at baseline, 85.7% vs. 65.8%; severe tricuspid regurgitation at baseline, 1% vs. 0.9%; degenerated valve was stented, 94.6% vs. 73.1%; mode of failure: stenosis (63.3% vs. 45.9%), regurgitation (8.8% vs. 35.1%) or mixed (27.9% vs. 18.9%)
Indirectness of population	No indirectness
Interventions	(n=147) Intervention 1: Transcatheter intervention (including TAVI-in-TAVI). Valve-in-valve transfemoral transcatheter aortic valve implantation (TAVI) procedure for degenerated aortic surgical bioprosthetic valves. Preoperative computed tomography scan performed in 100% of patients in this group. Duration NA - intervention procedure. Concurrent medication/care: 2.1% had percutaneous coronary intervetnon within the same hospital stay and 4.1% had coronary artery disease that was treated medically. Indirectness: No indirectness Further details: 1. Type of transcatheter intervention: Other transcatheter re-intervention procedure (TAVI valve-in-valve (surgical valve originally)). (n=111) Intervention 2: Surgical valve replacement with biological or mechanical valve - Surgical valve replacement with biological or mechanical valve - standard surgery. Redo surgical aortic valve replacement by sternotomy.18.9% received a mechanical valve. Experienced consultant cardiac surgeons performed all redo sternotomies and operations. Preoperative computed tomography scan performed in 94.6% of patients in this group. Duration NA - surgical procedure. Concurrent medication/care: 27% had concomitant surgery on the thoracic aorta, 0.9% had mitral valve decalcification, 9.0% had the Morrow procedure, 12.6% had concomitant coronary artery bypass grafting, 0.9% had percutaneous coronary intervention during same hospital stay and 2.7% had coronary artery disease that was medically managed. Indirectness: No indirectness

	Further details: 1. Type of transcatheter intervention: Not applicable
Funding	Academic or government funding (Grant from Leipzig Heart Institute)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSCATHETER INTERVENTION (INCLUDING TAVI-IN-TAVI) versus SURGICAL VALVE REPLACEMENT WITH BIOLOGICAL OR MECHANICAL VALVE (MAJORITY BIOLOGICAL) - STANDARD SURGERY Protocol outcome 1: All-cause mortality at Latest reported time-point - Actual outcome for Aortic valve: All-cause mortality at 12 months; HR; 1.93 (95%CI 0.7 to 5.36) (P-value: 0.75) , Comments: Adjusted HR reported as age not matched between the groups. Unclear exactly which factors adjusted for in the final results, but possibly the following: age, NYHA class III or IV at baseline, sex, STS-PROM, coronary artery disease at baseline ad mode of failure (regurgitation). Unadjusted 1 year all-cause mortality reported to be 8.8% vs. 9.9% (13/147 vs. 11/111). Used multiple Cox regression with backward selection using AIC criterion. Unclear whether age has been adjusted for in the final model as is not explicitly stated, but was considered in the model development process.; Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Performance: those in surgery group received concomitant surgical interventions; Indirectness of outcome: No indirectness ; Baseline details: Differences including age, NYHA class III or IV and surgical risk score specified in the protocol. Key confounder of age appears to have been considered in the multivariate model but unclear if the HR in final model is adjusted for age. NYHA class also adjusted for in model.; Key confounders: age; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Cardiac mortality at Latest reported time-point; Intervention-related mortality at 30 days; Quality of life at Latest reported time-point; Onset or exacerbation of heart failure at Latest reported time-point; Intervention-related stroke or TIA at 30 days; Intervention-related major bleeding at 30 days; Need for re-intervention at Latest reported time-point; Length of stay (following initial intervention) at Post-intervention; Re-hospitalisation at <12 months postoperatively; Re-hospitalisation at ≥12 months postoperatively; Intervention-related major vascular complications (defined as those requiring intervention for a vascular complication) at 30 days

Appendix E – Forest plots

E.1 Aortic valve

E.1.1 Transcatheter valve-in-valve vs. redo surgical aortic valve replacement for those with failing aortic bioprosthetic valves

Figure 2: All-cause mortality at 1-2 years – hazard ratio

Study or Subgroup	log[Hazard Ratio]	SE	Transcatheter VIV Total	Redo surgical AVR Total	Weight	Hazard Ratio IV, Fixed, 95% CI
1.1.1 HR						
Sedeek 2019	0.1655	0.3283	90	260	55.6%	1.18 [0.62, 2.25]
Silaschi 2017	0.3001	0.6335	71	59	14.9%	1.35 [0.39, 4.67]
Spaziano 2017	-0.1165	0.4618	78	78	28.1%	0.89 [0.36, 2.20]
Woitek 2020	0.6575	2.0635	147	111	1.4%	1.93 [0.03, 110.15]
Subtotal (95% CI)			**386**	**508**	**100.0%**	**1.12 [0.69, 1.81]**

Heterogeneity: Chi² = 0.43, df = 3 (P = 0.93); I² = 0%

Test for overall effect: Z = 0.46 (P = 0.64)

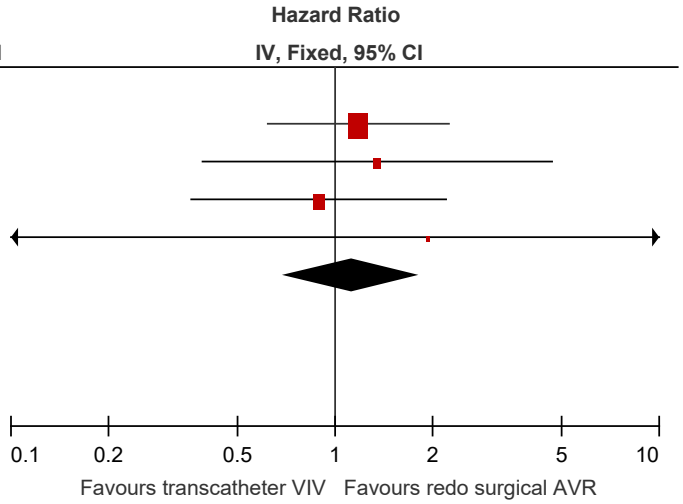


Figure 3: All-cause mortality at mean follow-up 794 days – dichotomous

Study or Subgroup	Transcatheter VIV Events	Total	Redo surgical AVR Events	Total	Risk Ratio M-H, Fixed, 95% CI
Deharo 2020	170	717	147	717	1.16 [0.95, 1.41]

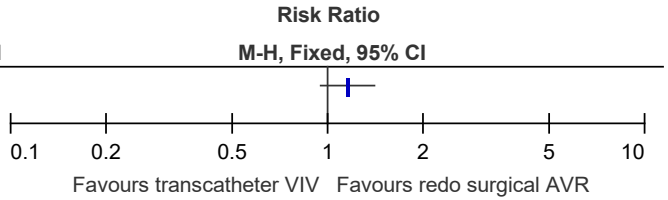


Figure 4: Cardiac mortality at 30 – 794 days

Study or Subgroup	Transcatheter VIV Events	Total	Redo surgical AVR Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Deharo 2020	82	717	78	717	96.0%	1.05 [0.78, 1.41]
Silaschi 2017	2	71	3	59	4.0%	0.55 [0.10, 3.21]
Total (95% CI)		**788**		**776**	**100.0%**	**1.03 [0.77, 1.38]**
Total events	84		81			

Heterogeneity: Chi² = 0.50, df = 1 (P = 0.48); I² = 0%

Test for overall effect: Z = 0.21 (P = 0.83)

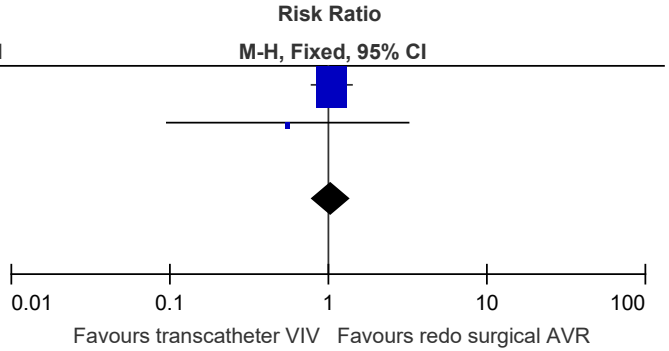


Figure 5: Intervention-related mortality at 30 days – operative-30 days

	Favours transcatheter VIV		Redo surgical AVR			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**
Deharo 2020	26	717	52	717	53.7%	0.50 [0.32, 0.79]
Ejiofor 2016	0	22	1	22	1.5%	0.33 [0.01, 7.76]
Malik 2020	5	710	35	710	36.2%	0.14 [0.06, 0.36]
Silaschi 2017	1	71	3	59	3.4%	0.28 [0.03, 2.59]
Spaziano 2017	3	78	5	78	5.2%	0.60 [0.15, 2.42]
Total (95% CI)		**1598**		**1586**	**100.0%**	**0.37 [0.25, 0.53]**
Total events	35		96			

Heterogeneity: Chi² = 6.24, df = 4 (P = 0.18); I² = 36%

Test for overall effect: Z = 5.22 (P < 0.00001)

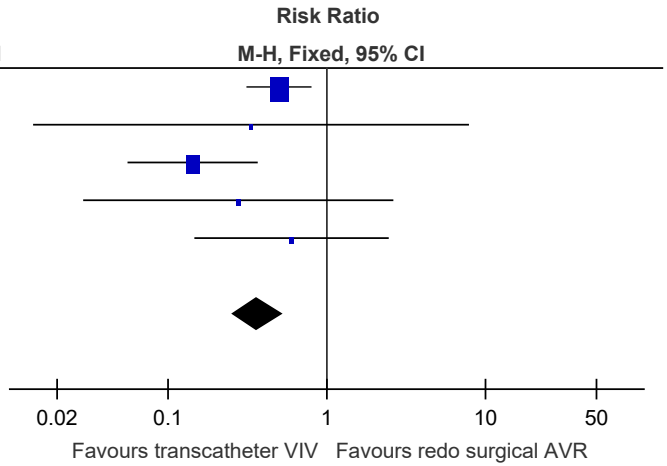


Figure 6: Onset or exacerbation of heart failure (hospitalisation for heart failure) at mean 794 days

	Transcatheter VIV		Redo surgical AVR		Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**M-H, Fixed, 95% CI**
Deharo 2020	199	717	144	717	1.38 [1.15, 1.67]

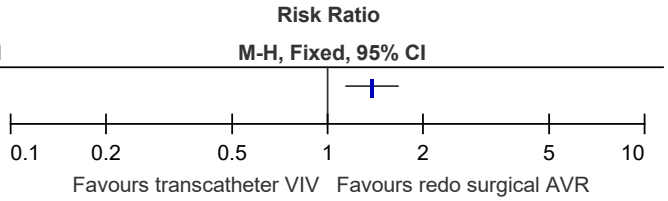
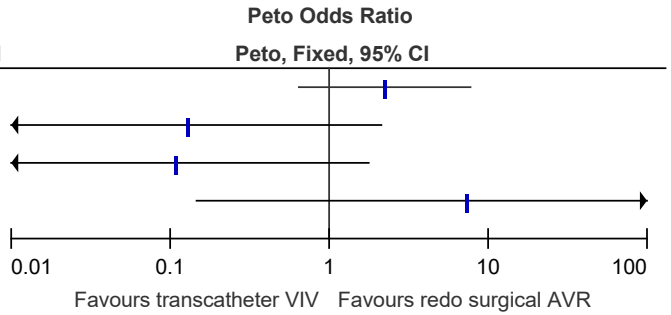


Figure 7: Intervention-related stroke or TIA at 30 days – postoperative-30 days

	Favours transcatheter VIV		Redo surgical AVR			Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI
Deharo 2020	7	717	3	717		2.24 [0.65, 7.76]
Ejiofor 2016	0	22	2	22		0.13 [0.01, 2.13]
Silaschi 2017	0	71	2	59		0.11 [0.01, 1.78]
Spaziano 2017	1	78	0	78		7.39 [0.15, 372.38]



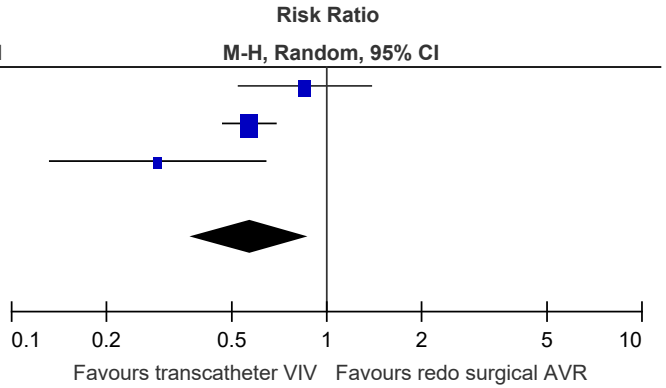
Note: Heterogeneity was considered to be present based on the point estimates of two of the studies opposing the other two studies. Pre-specified subgrouping strategies could not explain the heterogeneity as all studies fell within the same subgroups. Studies were therefore unpooled and results presented separately for each study, with results presented as Peto odds ratios due to there being zero events or a <1% event rate in all of the studies. Pooling results and using random effects was not performed as there are increased concerns about pooling non-randomised studies and the presence of unexplained heterogeneity further increases these concerns.

Figure 8: Intervention-related major bleeding at 30 days – in-hospital-30 days

	Transcatheter VIV		Redo surgical AVR			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Deharo 2020	29	717	34	717	32.1%	0.85 [0.53, 1.38]
Malik 2020	125	710	220	710	48.8%	0.57 [0.47, 0.69]
Silaschi 2017	7	71	20	59	19.2%	0.29 [0.13, 0.64]
Total (95% CI)		**1498**		**1486**	**100.0%**	**0.57 [0.37, 0.87]**
Total events	161		274			

Heterogeneity: Tau² = 0.09; Chi² = 5.42, df = 2 (P = 0.07); I² = 63%

Test for overall effect: Z = 2.57 (P = 0.01)



Note: despite an I^2 value of 63% suggesting some heterogeneity, this outcome was not downgraded for inconsistency as the point estimates all favour the transcatheter intervention and the heterogeneity present was not considered enough to warrant unpooling studies or downgrading for inconsistency. A random effects analysis was however used to capture the increased heterogeneity compared to most of the other outcomes included. Though transfusion was also reported for one study, the more general postoperative haemorrhage outcome was used in the analysis as it was unclear whether all transfusions were as a result of bleeding, and there may also have been other major bleeding events where transfusion was not performed. The outcome was downgraded for this in terms of indirectness. Pre-specified subgroup analyses could not be performed due to there being only three studies in the meta-analysis.

Figure 9: Need for reintervention (for paravalvular leak) – time-point unclear

	Transcatheter VIV		Redo surgical AVR			Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Ejiofor 2016	0	22	0	22		0.00 [-0.08, 0.08]

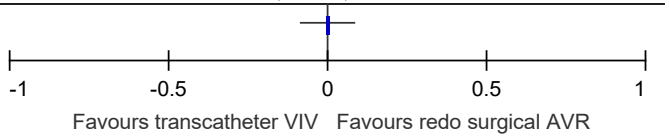


Figure 10: Re-hospitalisation at <12 months postoperatively – 30-180 days

	Transcatheter VIV		Redo surgical AVR			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Ejiofor 2016	5	22	3	22	61.3%	1.67 [0.45, 6.14]
Silaschi 2017	4	46	2	51	38.7%	2.22 [0.43, 11.55]
Total (95% CI)		**68**		**73**	**100.0%**	**1.88 [0.68, 5.23]**
Total events	9		5			

Heterogeneity: Chi² = 0.07, df = 1 (P = 0.79); I² = 0%

Test for overall effect: Z = 1.21 (P = 0.23)

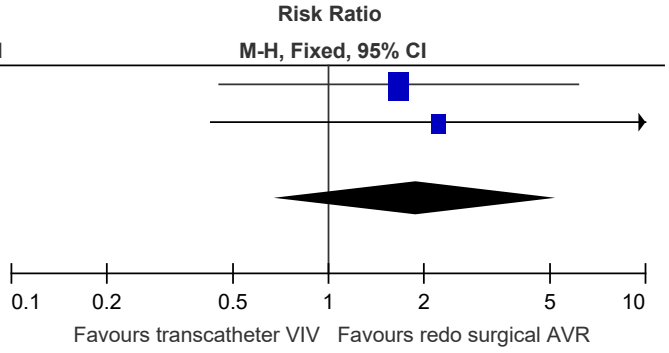
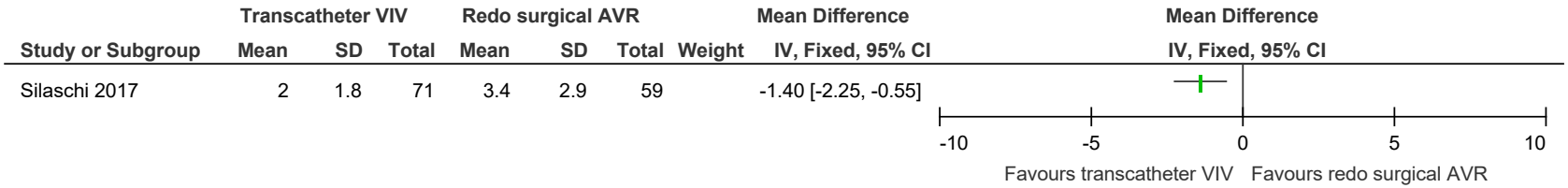


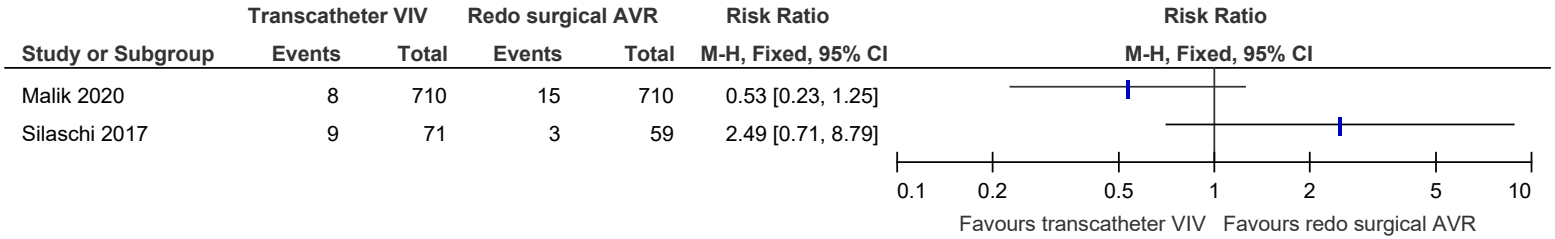
Figure 11: Intensive care unit length of stay



Note: one additional study reports data for this outcome as median (IQR), which is presented in the summary of results section. Data for hospital length of stay is also provided in the summary of results section, as none of the studies provided the results in a form that could be entered into Forest plots.

MIDs used to assess imprecision were calculated by multiplying the median control group final value SD (2.9) by 0.5 and were ±1.45.

Figure 12: Major vascular complications at 30 days – in-hospital-30 days



Note: Heterogeneity was considered to be present based on the opposing point estimates and high I^2 value. Pre-specified subgroup analyses could not be performed due to there being only two studies in the meta-analysis. Studies were therefore unpooled and results presented separately for each study.

E.2 Mitral valve

No evidence was identified.

E.3 Tricuspid valve

No evidence was identified.

Appendix F – GRADE tables

F.1 Aortic valve

Table 8: Clinical evidence profile: Transcatheter valve-in-valve vs. redo surgical aortic valve replacement for those with failing aortic bioprosthetic valves

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aortic valve: transcatheter valve-in-valve	redo surgical aortic valve replacement	Relative (95% CI)	Absolute		
All-cause mortality at latest reported time-point - HR (follow-up median 1-2 years)												
4	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	48/386 (12.4%)	74/508 (14.6%)	HR 1.12 (0.69 to 1.81)	16 more per 1000 (from 43 fewer to 102 more)	⊕OOO VERY LOW	CRITICAL
All-cause mortality at latest reported time-point - dichotomous (follow-up mean 794 days)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	170/717 (23.7%)	20.5%	RR 1.16 (0.95 to 1.41)	33 more per 1000 (from 10 fewer to 84 more)	⊕OOO VERY LOW	CRITICAL
Cardiac mortality at latest reported time-point (follow-up mean 30-794 days)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	84/788 (10.7%)	8.0%	RR 1.03 (0.77 to 1.38)	2 more per 1000 (from 18 fewer to 30 more)	⊕OOO VERY LOW	CRITICAL
Intervention-related mortality at 30 days (follow-up operative/in-hospital - 30 days)												

5	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	35/1598 (2.2%)	5.1%	RR 0.37 (0.25 to 0.53)	40 fewer per 1000 (from 50 fewer to 20 fewer)[3]	⊕⊕OO LOW	CRITICAL
Health-related quality of life at latest reported time-point												
0	No evidence available											CRITICAL
Onset or exacerbation of heart failure at latest reported time-point (follow-up mean 794 days)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	199/717 (27.8%)	20.1%	RR 1.38 (1.15 to 1.67)	76 more per 1000 (from 30 more to 135 more)	⊕OOO VERY LOW	CRITICAL
Intervention-related stroke or TIA at 30 days – 4 studies, not pooled due to unexplained heterogeneity												
Deharo 2020: All-cause stroke at 30 days (follow-up 30 days)												
1	randomised trials	very serious[1]	no serious inconsistency[4]	no serious indirectness	very serious[2]	none	7/717 (0.98%)	0.42%	OR 2.24 (0.65 to 7.76)	5 more per 1000 (from 1 fewer to 27 more)	⊕OOO VERY LOW	CRITICAL
Ejiofor 2016: Postoperative permanent stroke - postoperative (follow-up postoperative)												
1	randomised trials	very serious[1]	no serious inconsistency [4]	serious[5]	very serious[2]	none	0/22 (0%)	9.1%	OR 0.13 (0.01 to 2.13)	91 fewer per 1000 (from 231 fewer to 50 more)[3]	⊕OOO VERY LOW	CRITICAL
Silaschi 2017: Non-disabling or disabling stroke at 30 days (follow-up 30 days)												
1	randomised trials	very serious[1]	no serious inconsistency [4]	no serious indirectness	very serious[2]	none	0/71 (0%)	3.4%	OR 0.11 (0.01 to 1.78)	34 fewer per 1000 (from 88 fewer to 20 more)[3]	⊕OOO VERY LOW	CRITICAL
Spaziano 2017: Stroke according to VARC-2 at 30 days (follow-up 30 days)												

1	randomised trials	very serious[1]	no serious inconsistency [4]	no serious indirectness	very serious[2]	none	1/78 (1.3%)	0%	OR 7.39 (0.15 to 372.38)	13 more per 1000 (from 22 fewer to 48 more)[3]	⊕OOO VERY LOW	CRITICAL
Intervention-related major bleeding at 30 days (follow-up in-hospital-30 days)												
3	randomised trials	very serious[1]	no serious inconsistency	serious[6]	serious[2]	none	161/1498 (10.7%)	31.0%	RR 0.57 (0.37 to 0.87)	133 fewer per 1000 (from 40 fewer to 195 fewer)	⊕OOO VERY LOW	CRITICAL
Need for reintervention at latest reported time-point (reintervention due to paravalvular leakage) (follow-up unclear)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[7]	very serious[8]	none	0/22 (0%)	0%	RD 0 (-0.08 to 0.08)	0 fewer per 1000 (from 80 fewer to 80 more)[9]	⊕OOO VERY LOW	CRITICAL
Length of stay (following initial redo intervention) (Better indicated by lower values)												
0	No evidence available – some data available but reported in a format that could not be analysed. These results are presented in a separate table in the summary of results section.											IMPORTANT
ICU length of stay (following initial redo intervention) (follow-up postoperative; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2,10]	none	71	59	-	MD 1.4 lower (2.25 to 0.55 lower)	⊕OOO VERY LOW	IMPORTANT
Rehospitalisation at <12 months postoperatively - 30-180 days (follow-up 30-180 days)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	9/68 (13.2%)	8.8%	RR 1.88 (0.68 to 5.23)	77 more per 1000 (from 28 fewer to 372 more)	⊕OOO VERY LOW	IMPORTANT
Rehospitalisation at ≥12 months												
0	No evidence available											IMPORTANT

Intervention-related major vascular complications at 30 days (follow-up in-hospital-30 days) – 2 studies, not pooled due to unexplained heterogeneity												
Malik 2020: Intervention-related major vascular complications (those requiring intervention) - in-hospital (follow-up in-hospital)												
1	randomised trials	very serious[1]	no serious inconsistency [11]	serious[12]	very serious[2]	none	8/710 (1.1%)	2.1%	RR 0.53 (0.23 to 1.25)	10 fewer per 1000 (from 16 fewer to 5 more)	⊕OOO VERY LOW	IMPORTANT
Silaschi 2017: Intervention-related major vascular complications (VARC-2 definition) at 30 days (follow-up 30 days)												
1	randomised trials	very serious[1]	no serious inconsistency [11]	no serious indirectness	very serious[2]	none	9/71 (12.7%)	5.1%	RR 2.49 (0.71 to 8.79)	76 more per 1000 (from 15 fewer to 397 more)	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Risk difference used to manually calculate absolute effect as one study with zero events in one arm.
[4] For this outcome, the point estimate of two studies was in opposite direction to the other two studies. Prespecified subgrouping strategies could not explain these differences so results were not pooled. Differences may be due to small event numbers in all studies. Studies therefore kept separate rather than pooling.
[5] Unclear whether includes all of those up to 30 days as time-point is unclear
[6] One of the studies (79.8% weighting) defined the outcome as postoperative haemorrhage - unclear whether this covered the whole 30 day period specified in the protocol and also may include non-major bleeding events.
[7] Outcome poorly defined as only states that none required reintervention for paravalvular leakage - may have been other reasons that did require intervention but not reported. Time-point also unclear - may have covered immediate postoperative period only or 3 year follow-up.
[8] Assessment of imprecision based on sample size as zero events in both arms. Very serious imprecision as sample size <70.
[9] Risk difference used to manually calculate absolute effect as zero events in both arms of a single study.
[10] MIDs used to assess imprecision were ±1.45
[11] For this outcome, the point estimate of one study in opposite direction to the other study. Subgroup analyses could not be performed as only two studies. Studies therefore kept separate rather than pooling..
[12] Limited to in-hospital and does not necessarily cover 30 day time period in all patients. Also unclear whether all events were events that required intervention.

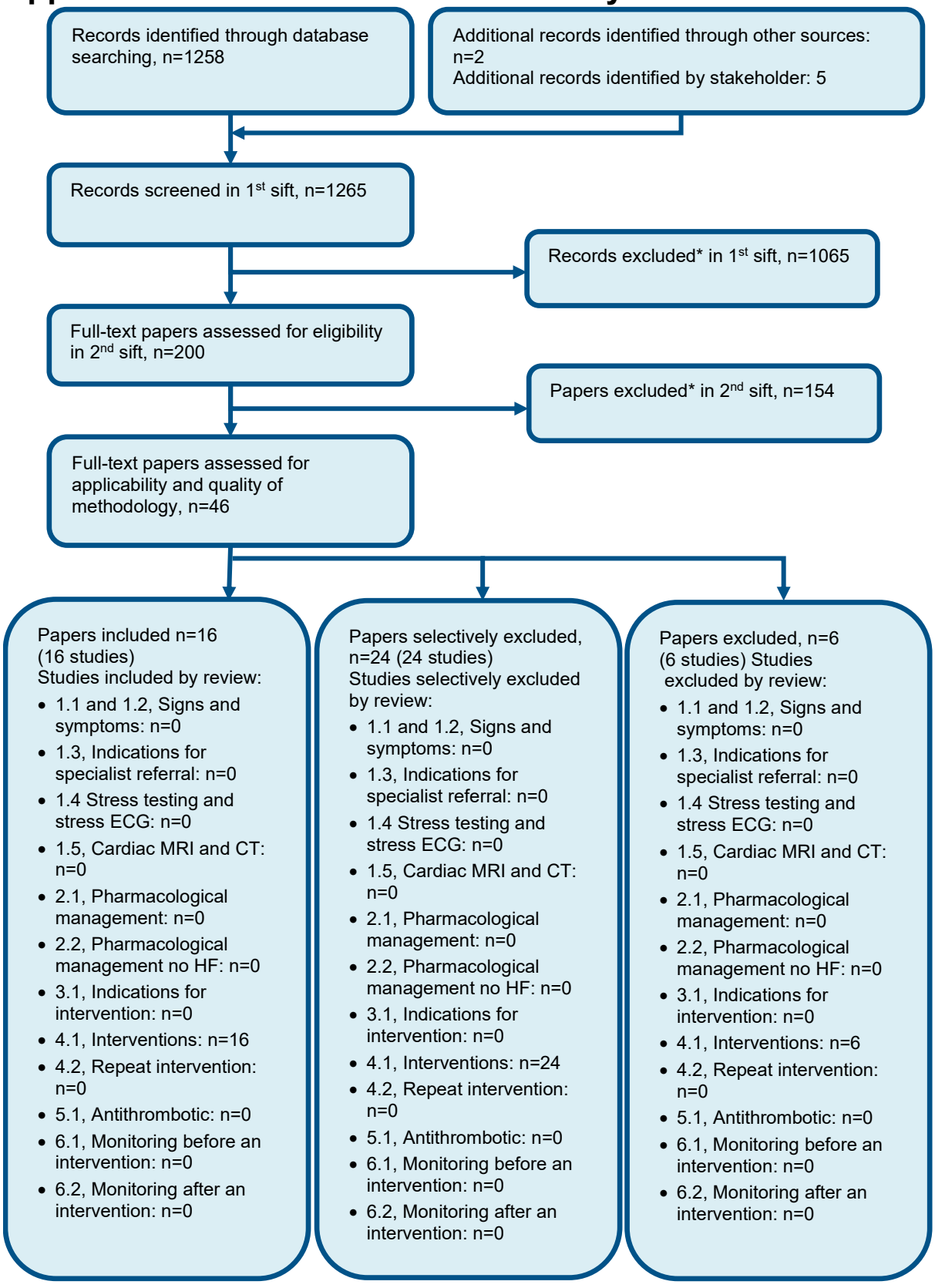
F.2 Mitral valve

No evidence was identified.

F.3 Tricuspid valve

No evidence was identified.

Appendix G – Economic evidence study selection



* Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix H Economic evidence tables

None.

Appendix I Health economic model

None.

Appendix J – Excluded studies

Clinical studies

Table 9: Studies excluded from the clinical review

Study	Exclusion reason
Argenziano 2010[1]	Incorrect interventions. Repeat repair intervention
Aslanabadi 2011[2]	Incorrect interventions. Repeat repair intervention
Ejiofor 2017[5]	Inappropriate comparison. Incorrect interventions
Ejiofor 2018[4]	Inappropriate comparison. Incorrect interventions
Erdem toker 2016[7]	Inappropriate comparison. Incorrect interventions
Erlebach 2015[8]	Non-randomised studies not accounting for age in analysis
Fukunaga 2012[11]	Inappropriate comparison. Incorrect interventions
Fukunaga 2014[10]	Inappropriate comparison. Incorrect interventions
Fukunaga 2018[9]	Incorrect interventions
Fukunaga 2018[12]	Inappropriate comparison. Incorrect interventions
Geidel 2014[13]	Incorrect interventions. Inappropriate comparison
Gosev 2015[14]	Incorrect interventions. Inappropriate comparison
Gozdek 2018[15]	Systematic review: study designs inappropriate
Greco 2020[16]	Incorrect interventions
Grubitzsch 2017[17]	Non-randomised studies not accounting for age in analysis
Hwang 2016[18]	Repeat repair intervention. Incorrect interventions
Jawitz 2020[19]	Inappropriate comparison. Incorrect interventions
Kamioka 2018[20]	Non-randomised studies not accounting for age in analysis
Kaneko 2014[21]	Incorrect interventions
Kawachi 1991[22]	Inappropriate comparison. Incorrect interventions
Kawachi 1994[23]	Inappropriate comparison. Incorrect interventions
Khalpey 2012[24]	Incorrect interventions
Kilic 2018[25]	Repeat repair intervention. Incorrect interventions
Kim 2018[26]	Re-intervention due to acute endocarditis. Inappropriate comparison. Incorrect interventions
Kothari 2016[27]	Inappropriate comparison. Incorrect interventions
Kreidel 2018[28]	Not review population. Repeat repair intervention. Incorrect interventions
Kumar 2004[29]	Inappropriate comparison. Incorrect interventions
Kwedar 2017[30]	Repeat repair intervention. Incorrect interventions
Lau 2006[31]	Incorrect interventions
Luciani 2006[33]	Inappropriate comparison. Incorrect interventions
Mehaffey 2018[36]	Inappropriate comparison. Incorrect interventions
Nalluri 2018[37]	Systematic review: study designs inappropriate
Neupane 2018[39]	Systematic review: study designs inappropriate
Oezpeker 2020[42]	Incorrect interventions
Phan 2016[43]	Systematic review: study designs inappropriate
Ranney 2016[44]	Incorrect study design. Inappropriate comparison. Incorrect interventions
Santarpino 2016[45]	Non-randomised studies not accounting for age in analysis
Sedeek 2019[46]	Non-randomised studies not accounting for age in analysis

Shehada 2018[48]	Systematic review is not relevant to review question or unclear PICO
Sugiura 2020[52]	Repeat repair intervention
Takagi 2019[53]	Systematic review: study designs inappropriate
Tam 2018[54]	Systematic review: study designs inappropriate
Tourmousoglou 2015[55]	Incorrect study design - narrative review
Tsubota 2020[56]	Not review population. Incorrect interventions
Ussia 2011[57]	Not review population. Inappropriate comparison. Incorrect interventions
Varrica 2020[58]	Incorrect interventions
Webb 2017[59]	Incorrect study design - editorial
Yoon 2017[61]	Inappropriate comparison. Incorrect interventions

Health Economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2005 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

None.

Appendix K – Research recommendations – full details

K.1 Aortic valves

K.1.1 Research recommendation

What is the clinical and cost-effectiveness of transcatheter intervention compared with surgical redo intervention for adults with failing biological prosthetic aortic valves when either procedure is suitable?

K.1.2 Why this is important

The number of patients whose aortic valve has been replaced with tissue valve prostheses has increased in recent years. It is known that a significant percentage of these prostheses fail causing life threatening illness. Until recently, redo heart surgery was the only available treatment. Now that transcatheter therapy for failing heart valve tissue prostheses is also available, it is important that trials provide the evidence for the safer and most cost-effective option.

K.1.3 Rationale for research recommendation

Importance to 'patients' or the population	Patients suffering with degeneration of a tissue aortic valve prosthesis have already undergone potentially life changing major heart surgery. The effects of a malfunctioning prosthesis are life threatening and patients require a treatment that is not just safe and cost effective but is durable thus mitigating the need for further treatment or lifetime hospital-based surveillance.
Relevance to NICE guidance	The comparison between transcatheter and surgical redo intervention for patients with failing biological prosthetic aortic valves was considered in this guideline; however, only non-randomised studies were identified, meaning the evidence was not considered to be strong enough to determine whether one was associated with better outcomes than the other and a recommendation was made in line with current practice to consider either based on the specific characteristics of each patient. Answering this question with a randomised controlled trial would provide more robust evidence that may allow any differences between the two treatments to be identified and used to strengthen or inform changes to recommendations. At the present time patients with degenerating tissue aortic valve prostheses are increasingly being referred for transcatheter treatment. The attraction of avoiding open surgery is obvious but this change of practice is not backed up by good evidence of safety, clinical effectiveness or durability. Strong evidence from a RCT may enable NICE to recommend one treatment over the other with confidence.

Relevance to the NHS	Over the past 15 years, the median age of patients receiving tissue aortic prostheses in the NHS has fallen resulting in a marked increase in the numbers who receive this type of prosthesis. This has resulted in a significant increase in patients requiring treatment for degeneration of tissue prosthesis. When more than 1 treatment for this complication is available, it is important that NICE is able to recommend a treatment to the NHS that is safe and cost-effective and one that minimises future healthcare needs for patients.
National priorities	None known
Current evidence base	Although five studies were included in the review for this comparison, all of these were retrospective cohort studies with certain characteristics differing between study arms and not all being adjusted for. The lack of randomised controlled trials or adequately adjusted non-randomised studies in this area meant that there was not considered to be sufficient evidence to assess differences between the two interventions and a recommendation was made to consider either based on specific patient characteristics, which was in line with current practice. Evidence from randomised controlled trials comparing these two interventions for redo aortic valve intervention would provide more robust evidence and allow the two interventions to be compared more accurately in patients that are similar to each other and it was agreed that a randomised controlled trial should be possible..
Equality considerations	Currently age has a strong influence on choice of treatment with older patients more likely to be referred for non-surgical treatment. Age needs to be considered in the design of possible RCTs.

K.1.4 Modified PICO table

Population	<u>Inclusion</u> Adults aged 18 years and over with degeneration of surgically implanted biological aortic valve prostheses requiring repeat intervention. <u>Exclusion</u> • Children (aged <18 years) • Adults with congenital heart disease (other than bicuspid aortic valves) • Re-intervention due to acute endocarditis • Re-intervention for paravalvar regurgitation
Intervention	Redo transcatheter aortic valve intervention (TAVI)

Comparator	Redo surgical aortic valve replacement with biological or mechanical valve
Outcome	Primary outcomes All-cause mortality at >12 months; cardiac mortality at >12 months; intervention-related mortality at 30 days; health-related quality of life at >12 months; onset or exacerbation of heart failure at >12 months; intervention-related stroke or TIA at 30 days; intervention-related major bleeding at 30 days; need for reintervention at >12 months. Secondary outcomes Length of stay (following repeat intervention); re-hospitalisation at ≤12 months and >12 months; intervention-related major vascular complications at 30 days (defined as those requiring intervention for a vascular complication)
Study design	Adequately powered randomised controlled trial
Timeframe	Long term
Additional information	None

K.2 Mitral valves

K.2.1 Research recommendation

What is the clinical and cost-effectiveness of transcatheter intervention compared with surgical redo intervention for adults with failing biological prosthetic mitral valves when either procedure is suitable?

K.2.2 Why this is important

The number of patients whose mitral valve has been replaced with tissue valve prostheses has increased in recent years. It is known that a significant percentage of these prostheses fail causing life threatening illness. Until recently, redo heart surgery was the only available treatment. Now that transcatheter therapy for failing heart valve tissue prostheses is also available, it is important that trials provide the evidence for the safer and most cost-effective option.

K.2.3 Rationale for research recommendation

Importance to 'patients' or the population	Patients suffering with degeneration of a tissue mitral valve prosthesis have already undergone potentially life changing major heart surgery. The effects of a malfunctioning prosthesis are life threatening and patients require a treatment that is not just safe and cost effective but is durable thus mitigating the need for further treatment or lifetime hospital-based surveillance.
Relevance to NICE guidance	The comparison between transcatheter and surgical redo intervention for patients with failing biological prosthetic mitral valves was considered in this guideline; however, no

	comparative studies were identified covering the mitral valve population, meaning there was no evidence on which to base recommendations. Answering this question would provide comparative evidence that may allow recommendations to be made for redo mitral valve intervention for those with biological prosthetic valves following their initial replacement intervention. At the present time patients with degenerating tissue mitral valve prostheses are increasingly being referred for transcatheter treatment. The attraction of avoiding open surgery is obvious but this change of practice is not backed up by good evidence of safety, clinical effectiveness or durability. Strong evidence from a RCT may enable NICE to recommend one treatment over the other with confidence.
Relevance to the NHS	Over recent years, the median age of patients receiving tissue prostheses in the NHS has fallen resulting in an increase in the numbers who receive this type of prosthesis. This has resulted in a significant increase in patients requiring treatment for degeneration of tissue prosthesis. When more than 1 treatment for this complication is available, it is important that NICE is able to recommend a treatment to the NHS that is safe and cost-effective and one that minimises future healthcare needs for patients.
National priorities	None known
Current evidence base	No comparative studies, even non-randomised, were identified for repeat intervention in those with mitral valve disease and biological prosthetic valves as a result of their initial replacement intervention, meaning no recommendations were made for repeat intervention in this population. Studies comparing outcomes between transcatheter and surgical redo intervention in this population would therefore allow the two procedures to be compared in similar patients and possibly allow recommendations to be made for this population. Though it was noted that randomised controlled trials would provide more robust evidence than non-randomised studies that are limited by differences in characteristics between arms due to the selection process, it was highlighted that transcatheter repeat intervention for biological prosthetic mitral valves is not as well established as it is for biological prosthetic aortic valves and there is a lack of comparative evidence even in the form of non-randomised studies for the mitral population. Therefore, a randomised controlled trial or non-randomised cohort study with adjustment for relevant confounders, to address some of the concerns about confounding in non-randomised studies, is suggested.

Equality considerations	Currently age has a strong influence on choice of treatment with older patients more likely to be referred for non-surgical treatment. Age needs to be considered in the design of possible RCTs.

K.2.4 Modified PICO table

Population	Inclusion Adults aged 18 years and over with degeneration of surgically implanted biological mitral valves requiring repeat intervention. Exclusion • Children (aged <18 years) • Adults with congenital heart disease (other than bicuspid aortic valves) • Re-intervention due to acute endocarditis • Re-intervention for paravalvar regurgitation
Intervention	Redo transcatheter mitral valve intervention
Comparator	Redo surgical mitral valve replacement with biological or mechanical valve
Outcome	Primary outcomes All-cause mortality at >12 months; cardiac mortality at >12 months; intervention-related mortality at 30 days; health-related quality of life at >12 months; onset or exacerbation of heart failure at >12 months; intervention-related stroke or TIA at 30 days; intervention-related major bleeding at 30 days; need for reintervention at >12 months. Secondary outcomes Length of stay (following repeat intervention); re-hospitalisation at ≤12 months and >12 months; intervention-related major vascular complications at 30 days (defined as those requiring intervention for a vascular complication)
Study design	Adequately powered randomised controlled trial or non-randomised comparative cohort study with adjustment or matching for the following confounders: • Age and all other confounders identified in the study
Timeframe	Long term
Additional information	None

K.3 Tricuspid valves

K.3.1 Research recommendation

What is the clinical and cost-effectiveness of transcatheter intervention compared with surgical redo intervention for adults with failing biological prosthetic tricuspid valves or failing repaired native tricuspid valves when either procedure is suitable?

K.3.2 Why this is important

In the NHS, the number of tissue aortic valve devices being implanted into younger patients is increasing rapidly. As these have a limited life span, the number of patients who will need repeat procedures is also increasing. It is important therefore the NHS supports and funds the most clinically and cost effective procedure.

K.3.3 Rationale for research recommendation

Importance to 'patients' or the population	Transcatheter interventions are non-surgical and therefore patients are spared an incision and relatively long stay in hospital. Early morbidity is as expected less than in patients undergoing redo surgery. However as this is new technology, the long-term effects and durability of the devices are unknown. Recent observational studies suggest medium clinical outcomes are markedly inferior in patients receiving a transcatheter rather than a surgical device.
Relevance to NICE guidance	The comparison between transcatheter and surgical redo intervention for patients with failing biological prosthetic tricuspid valves was considered in this guideline; however, no comparative studies were identified covering the tricuspid valve population, meaning there was no evidence on which to base recommendations. Answering this question would provide comparative evidence that may allow recommendations to be made for redo tricuspid valve intervention for those with biological prosthetic valves following their initial replacement intervention.
Relevance to the NHS	In the NHS, the number of tissue aortic valve devices being implanted into younger patients is increasing rapidly. As these have a limited life span, the number of patients who will need repeat procedures is also increasing. It is important therefore the NHS supports and funds the most clinically and cost-effective procedure.
National priorities	Because of the high cost of the transcatheter devices (relative to surgical devices), commissioning of all transcatheter valve therapy is a big issue within the NHS. In the absence of strong evidence, the NHS is unlikely to commission relatively new procedures.

Current evidence base	No comparative studies, even non-randomised, were identified for repeat intervention in those with tricuspid valve disease and biological prosthetic valves as a result of their initial replacement intervention, meaning no recommendations were made for repeat intervention in this population. Studies comparing outcomes between transcatheter and surgical redo intervention in this population would therefore allow the two procedures to be compared in similar patients and possibly allow recommendations to be made for this population.
Equality considerations	Many of the patients with degeneration of tissue aortic valve prostheses are older adults who are frail and unsuitable for surgery. They would not be eligible for any proposed research trial.

K.3.4 Modified PICO table

Population	Inclusion Adults aged 18 years and over with degenerated biological tricuspid valves or failing repaired native tricuspid valves requiring repeat intervention. Exclusion • Children (aged <18 years) • Adults with congenital heart disease (other than bicuspid aortic valves) • Re-intervention due to acute endocarditis • Re-intervention for paravalvar regurgitation
Intervention	Redo transcatheter tricuspid valve intervention
Comparator	Redo surgical tricuspid valve replacement with biological or mechanical valve
Outcome	Primary outcomes All-cause mortality at >12 months; cardiac mortality at >12 months; intervention-related mortality at 30 days; health-related quality of life at >12 months; onset or exacerbation of heart failure at >12 months; intervention-related stroke or TIA at 30 days; intervention-related major bleeding at 30 days; need for reintervention at >12 months. Secondary outcomes

	Length of stay (following repeat intervention); re-hospitalisation at ≤12 months and >12 months; intervention-related major vascular complications at 30 days (defined as those requiring intervention for a vascular complication)
Study design	Non-randomised comparative cohort study with adjustment or matching for the following confounders: • Age and all other confounders identified by the study
Timeframe	Long term
Additional information	None