A report on treatment options for pulmonary valve replacement for Universitätsklinikum Schleswig-Holstein/Campus Kiel

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LIST OF ABBREVIATIONS

AEs	Adverse effects
CDSR	Cochrane Database of Systematic Reviews
CI	Confidence interval
CPG	Clinical practice guideline
CRD	Centre for Reviews and Dissemination
DARE	Database of Abstracts of Reviews of Effects
ESA	Edwards SAPIEN®
FAQ	Frequently asked question
GIN	Guidelines International Network
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICU	Intensive care unit
IE	Infective endocarditis
KSR	Kleijnen Systematic Reviews
LVEF	Left ventricular ejection fraction
MD	Mean difference
MF	Medtronic Freestyle®
MM	Medtronic Melody®
NICE	National Institute for Health and Care Excellence
NR	Not reported
NYHA	New York Heart Association
OR	Odds ratio
PICOS	Participants, intervention, comparators, outcomes, and study design
PPVR	Percutaneous pulmonary valve replacement
PVD	Pulmonary valve dysfunction
PVR	Pulmonary valve replacement
RCT	Randomised controlled trial
RR	Relative risk/risk ratio
RVOT	Right ventricular outflow tract
SDM	Shared decision making
SF-36	36-item short form questionnaire
SMD	Standardised mean difference
SPVR	Surgical pulmonary valve replacement
SR	Systematic review
SVD	Structural valve deterioration
UKSH	Universitätsklinikum Schleswig-Holstein

1. PROJECT OBJECTIVES

A key aim of the research project “Making SDM a reality” is to inform patients as part of shared decision making (SDM).

Kleijnen Systematic Reviews (KSR) Ltd has prepared an evidence report with a synthesis of the evidence of the relevant treatment options and types of grafts for pulmonary valve replacement (PVR).

2. METHODS

2.1 INCLUSION CRITERIA

The frequently asked questions (FAQs) underpinning the literature searches were developed with clinical experts at Universitätsklinikum Schleswig-Holstein (UKSH)/Campus Kiel. These questions reflect the relevant characteristics of participants, intervention, comparators, outcomes, and study design (PICOS), see Table 1. Systematic reviews (SRs) evaluated herein aim to inform clinicians, patients, researchers, and health policy makers on relevant evidence pertaining to the pulmonary valve replacement and different types of grafts used.

Table 1: Inclusion and exclusion criteria

	Included	Excluded
Population	Patients aged 14 or older with pulmonary valve dysfunction and indication for pulmonary valve replacement (examples: Tetralogy of Fallot, Truncus arteriosus; after Ross Procedure, pulmonary valve stenosis and/or pulmonary regurgitation)	Children or adolescents <14 years old; large native or patch-enlarged right ventricular outflow tract with dimensions > 35 mm; high risk for coronary compression; low body weight approx. <30 kg
Intervention	1. Percutaneous pulmonary valve replacement (porcine or bovine grafts) 2. Surgical pulmonary valve replacement (homografts, porcine or bovine grafts)	Mechanical grafts
Comparator	No intervention	None
Outcomes	1. Mortality (all-cause mortality, cause-specific mortality/treatment related mortality) 2. Resolution of symptoms, function, exercise capacity 3. Quality of life 4. Hospitalisation, length of ICU stay 5. Time to re-intervention 6. Return to usual activity 7. Adverse events/side effects (specifically endocarditis) 8. Valve durability/structural valve deterioration	None
Study design	Systematic reviews, health technology assessments, clinical practice guidelines; primary research	Narrative reviews; expert opinions; letters
ICU = intensive care unit; PVR = pulmonary valve replacement		

2.2 FREQUENTLY ASKED QUESTIONS

The FAQs were identified:

1. What does the treatment involve?

2. Will the treatment prolong my life?
3. Will it help my symptoms?
4. How long will treatment effect last? Will it help maintain remission of my disease?
5. How will treatment impact my quality of life?
6. Will it impact my risk of having to go into the hospital?
7. When will I recover?
8. What are the risks or side effects (specifically endocarditis)?
9. Are there long-term negative effects of treatment to be expected?
10. How long will the graft last?

2.3 LITERATURE SEARCHES

Literature searches were conducted to identify systematic reviews and guidelines of surgical and percutaneous pulmonary valve replacement. The search strategies were based on those used in a previous SDM review conducted in 2020 and expanded to include additional terms for the three main categories of grafts (porcine, bovine and homografts). Search terms were developed specifically for each database and the keywords adapted according to the configuration of each database. Searches were not limited by language or publication status.

2.4 SEARCH SOURCES

The following systematic review/health technology assessment (HTA) specific databases were searched in April 2021 from 2016 to the most recent date available:

- Cochrane Database of Systematic Reviews (CDSR) (Wiley): up to 2021/04/Iss4
- Database of Abstracts of Reviews of Effects (DARE) (CRD): up to 31 Mar 2015
- Health Technology Assessment (HTA) database (CRD): up to 31 Mar 2018
- INAHTA International HTA database (https://database.inahta.org/): up to 2021/04/14
- KSR Evidence (Internet) (https://ksrevidence.com/): up to 2021/04/14
- Epistemonikos (Internet) (https://www.epistemonikos.org/): up to 2021/04/15

The following guidelines resources were searched in April 2021 from 2016 to the most recent date available:

- NICE Guidance (Internet) (https://www.nice.org.uk/guidance): up to 2021/04/13
- ECRI Guidelines Trust (Internet) (https://guidelines.ecri.org/): up to 2021/04/15
- NICE Evidence (Internet) (http://www.evidence.nhs.uk/): up to 2021/04/14
- TRiP Database (Internet) (https://www.tripdatabase.com/): up to 2021/04/14

- Guidelines International Network (GIN) (Internet) (https://www.g-i-n.net/home): up to 2021/04/13

Full details of all search strategies are presented in Appendix 1.

2.5 HANDLING OF CITATIONS

Identified references from the bibliographic database searches were downloaded into EndNote 20 bibliographic management software for further assessment and handling.

2.6 STUDY SELECTION AND DATA EXTRACTION

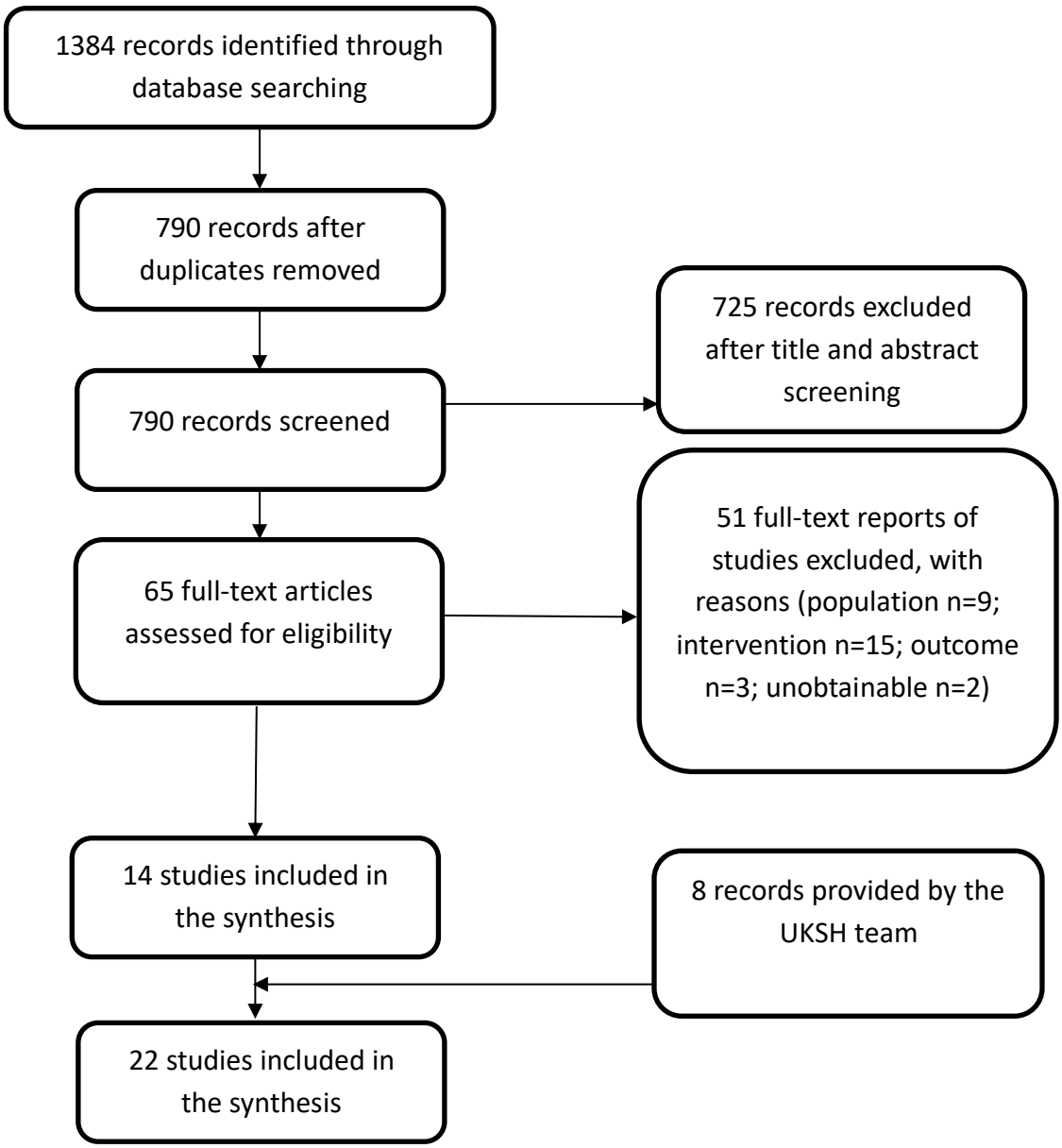
Two independent reviewers screened titles and abstracts of all records identified by the electronic searches. Any disagreements between the reviewers were settled through a consensus. For potentially eligible SRs, clinical practice guidelines (CPG), or primary studies, full-text versions were obtained, and screened against inclusion and exclusion criteria by these same two independent reviewers. For each study, data were extracted by one reviewer and another reviewer validated the entries. Any disagreements were resolved through a discussion.

3. RESULTS

3.1 LITERATURE SEARCHES AND INCLUSION ASSESSMENT

Searches were conducted on 18 November 2020 and re-run in April 2021 to identify all relevant SRs, HTAs, or CPGs. A total of 1384 records were retrieved from the electronic searches. After the removal of duplicate records 790 titles and abstracts were screened by two independent reviewers. After screening of 65 full-text papers, fourteen met the inclusion criteria. Additional eight records were provided by the UKSH Team. Those mainly observational studies were not identified by our searches geared towards SRs, HTAs, or CPGs. A summary of the study selection process according to modified PRISMA reporting guidelines is reported in Figure 1.[1]

Figure 1: Study selection process



3.2 OVERVIEW OF INCLUDED STUDIES

Overall, twelve SRs, one CPG, and nine observational studies were eligible for inclusion. Table 2 summarises the sources of evidence used to answer the ten FAQs. These SRs and CPG included predominantly observational evidence i.e. case reports, case control and cohort studies. Quantitative evidence from direct comparisons, i.e. percutaneous pulmonary valve replacement (PPVR) versus surgical pulmonary valve replacement (SPVR), was available to answer the respective FAQs. For FAQ 5, no numerical results were available, and available evidence was summarised narratively. Durability of different types of valves were compared under FAQ 10.

Table 2: Evidence sources

Study	Evidence type	Intervention or valve type	FAQ1: What does the treatment involve?	FAQ2: Will the treatment prolong my life?	FAQ3: Will it help my symptoms?	FAQ4: How long will treatment effect last? Will it help maintain remission of my disease?	FAQ5: How will treatment impact my quality of life?	FAQ6: Will it impact my risk of having to go into the hospital?	FAQ7: When will I recover?	FAQ8 & 9: What are the risks or side effects; Are there long-term negative effects of	FAQ10:How long will the graft last?
Ribeiro 2020[2]	SR	PPVR SPVR		✓				✓		✓	
Zhou 2019[3]	SR	PPVR SPVR	✓	✓		✓		✓		✓	
McRae 2017[4]	SR	PPVR SPVR		✓	✓		✓			✓	
Ran 2019[5]	SR	PPVR		✓		✓				✓	
Lehner 2019[6]	SR	PPVR/ESA, MM		✓						✓	
Abdelghani 2018[7]	SR	PPVR/MM		✓				✓		✓	
Chatterjee 2017[8]	SR	PPVR		✓				✓		✓	
NICE 2013[9]	CPG	PPVR	✓								
Botrel 2013[10]	SR	MM ESA								✓	

Sharma 2017[11]	SR	MM Contegra								✓	
Van den Eynde 2020[12]	SR	MF									✓
Dunne 2015[13]	SR	Homograft, bovine pericardial, Contegra, Edwards Prima, Edwards porcine conduit, MF, MM, Hancock II, Perimount, Toronto									✓
Cocomello 2019[14]	Obs. study	Homografts, bioprosthesis									✓
Bell 2018[15]	Obs. study	Homografts, bioprosthesis									✓
Gröning 2019[16]	Obs. study	Homografts, Contegra								✓	
McElhinney 2018[17]	Obs. study	Homografts, Contegra								✓	
Georgiev 2020[18]	Obs. study	MM, homografts, Hancock, Contegra, and others		✓						✓	

Waqanivavalagi 2020[19]	SR	Decellularized valves, standard tissue conduits		✓				✓			
Nordmeyer 2019[20]	Obs. study	MM		✓						✓	
Shahanavaz 2020[21]	Obs. study	Stented bioprostheses, conduit homografts, stentless porcine, and other valved, nonvalved stentless conduits				✓				✓	
Sabate Rotes 2014[22]	Obs. study	Homograft, porcine, pericardial SPVR		✓				✓			
Mery 2016[23]	Obs. study	Homograft, bovine jugular, heterograft								✓	

CPG = clinical practice guideline; ESA = Edwards Sapien; MF = Medtronic Freestyle; MM = Medtronic Melody; NICE = National Institute for Health and Care Excellence; Obs. study = observational study; PPVR = percutaneous pulmonary valve replacement; SPVR = surgical pulmonary valve replacement; SR = systematic review

3.3 FAQ 1: What does the treatment involve?

This section covers the two treatment options for pulmonary valve dysfunction, i.e., surgical pulmonary valve replacement (SPVR) or percutaneous pulmonary valve replacement (PPVR). These two options and a description of the condition are given in Table 3. This section also briefly describes the condition i.e., pulmonary valve dysfunction itself.

Table 3: Description of treatments for pulmonary valve dysfunction

Pulmonary valve dysfunction
Pulmonary valve dysfunction (PVD) is the term that refers to abnormalities of the pulmonary valve (one of the valves in the heart which lies between the lower right heart chamber and the pulmonary artery) and the right ventricular outflow tract (RVOT). This dysfunction often occurs as part of complex congenital (present from birth) heart conditions that causes blood to circulate abnormally between the heart and the lungs.[9] When left untreated, PVD can cause varying degrees of right ventricular hypertrophy (heart chamber enlargement) and reduce a person's lifespan consequently. Most frequent indications for PVD include Tetralogy of Fallot (a combination of four congenital abnormalities such as ventricular septal defect, pulmonary valve stenosis (an abnormal narrowing), a misplaced aorta (largest artery in the human body) and a thickened right ventricular wall); truncus arteriosus (a structural defect of the heart present since birth); and patients after Ross Procedure (a cardiac surgery where a dysfunctional aortic valve is replaced with the person's own pulmonary valve).
Percutaneous pulmonary valve replacement (PPVR)
PPVR is a less invasive intervention than open heart surgery.[3] PPVR aims to improve pulmonary valve function and circulation to the lungs while reducing the pressure in the right ventricle; and delaying the need for further surgical reintervention.[9] Several types of PPVR exist e.g. Medtronic Melody valve or Edwards Sapien. During PPVR, a heart surgeon inserts a catheter (a soft hollow tube) in a large blood vessel and guides it to the heart. The procedure is undertaken without the need for general anaesthesia, cardiopulmonary bypass support (a machine temporarily takes over the function of the heart and lungs by adding oxygen to the blood, moving blood through the body, and removing carbon dioxide) and avoiding median sternotomy (opening of the chest bone).[3]
Surgical pulmonary valve replacement (SPVR)
SPVR involves an open-heart surgery and opening of the chest bone. This procedure is performed under anaesthesia so that a patient does not feel any pain. During the procedure, the heart is temporarily stopped, and the patient is placed on cardiopulmonary bypass support described above. After SPVR, a patient will typically spend a day or more in the intensive care unit followed by a regular hospital room for a few more days. During that time, a patient will get fluids, nutrition and medications intravenously. After a discharge and during the recovery process, a patient must follow certain instructions, look after wounds/incisions, take medications, and manage pain as well as other potential side effects. There are two types of valves used during SPVR - mechanical valve and biological valve. With regards to mechanical valves, a patient will need anticoagulants (blood thinning

medications) for the rest of his/her life. However, biological valves degenerate over time and often need to be replaced; and that necessitates another surgical intervention. This is discussed in depth under FAQ 10 (please also refer to Table 10).

3.4 FAQ 2: WILL THE TREATMENT PROLONG MY LIFE?

This section explains whether specific types of interventions, i.e. PPVR or SPVR will prolong life expectancy. This section also describes the evidence for mortality following PPVR or SPVR. None of the included systematic reviews reported overall survival but one observational study did. Three systematic reviews compared PPVR and SPVR and reported the numbers of deaths either during hospitalisation, within 30 days of the procedure, or during follow-up. The results are presented in Table 4.

The systematic review by Ribeiro et al. 2020 searched the literature up to January 2019 and included studies of any design comparing PPVR and SPVR.[2] It included 18 studies in the meta-analysis, all of which were observational. Risk of bias was assessed using a tool for randomised controlled trials (RCTs) which was not appropriate for observational study designs, and all studies were judged to be at a high risk of bias. The two groups were similar with regards to gender (59% male) and age (mean ages of 21.9 and 19.7 years) although the PPVR patients were less likely to have a native right ventricle outflow tract (RVOT) or transannular patch (16% vs. 60%) and pulmonary regurgitation as an indication (22% vs. 57%) or preprocedural (63% vs. 80%). There was no evidence of a difference between PPVR and SPVR in mortality during or within 30 days of admission (odds ratio [OR] 0.56, 95% confidence interval [CI] 0.19 to 1.59, 11 studies) or during follow-up ranging from 1.6 to 8.8 years (OR 0.78, 95% CI 0.30 to 2.00, six studies). The overall quality of the evidence was very low due to high risk of bias and inconsistency.

Another systematic review by Zhou et al. 2019 included 11 retrospective observational studies directly comparing PPVR and SPVR.[3] The literature was searched up to December 2019. Risk of bias was assessed using the Newcastle Ottawa scale and studies scoring six or more were considered to be of high quality. All studies were considered to be of high quality (mean score of 6.8) by the review. However, given that there were no randomised trials, all studies were retrospective and only two attempted to balance the groups using propensity score matching, then the overall quality of the evidence was very low due to high risk of bias and imprecision. Mean ages ranged from 12 to 31.5 years (two of the 10 SPVR studies (20%) included adolescents aged <14); and 59.6% of patients were male. Results showed that mortality in hospital (OR 0.18, 95% CI 0.03 to 0.98, three studies) and during the follow-up period of up to 89 months (OR 0.43, 95% CI 0.22 to 0.87, 11 studies) was reduced with PPVR compared to SPVR. It is therefore worth mentioning these effect estimates are inclusive of the population which is outside the scope of PICO (Table 1).

McRae et al. 2017 performed a systematic review and meta-analysis evaluating PPVR and SPVR in patients with pulmonary regurgitation after repaired tetralogy of Fallot.[4] Studies of any design published between 1995 and May 2016 reporting on patient outcomes after

surgical, transcatheter or hybrid PVR were included. The review included studies evaluating each type of procedure, not ones which directly compared them. The meta-analyses pooled outcomes for each procedure separately but did not perform any statistical comparisons between them. It was not a pooled analysis of studies comparing PPVR with SPVR. There were 47 PPVR and 85 SPVR studies, the PPVR studies were a mix of prospective and retrospective cohort designs and the SPVR studies were mostly retrospective but did include one RCT comparing SPVR with and without right vein remodelling. Risk of bias was not assessed in the review, but the overall quality of the evidence is considered very low due to the inclusion of retrospective study designs and the lack of direct comparison between PPVR and SPVR (indirectness). Mean patient age ranged from five to 59 years. Similarly, 17 of the 85 SPVR studies (20%) included children and adolescents aged <14, which is outside the scope of PICO (Table 1). Mortality rates within the first 30 days after PVR were 0.3% (range 0 to 1.6%) with PPVR and 1% (range 0 to 10%) with SPVR.

Four systematic reviews only evaluated PPVR using prospective and retrospective cohort studies.[5-8] Two evaluated the Melody and Edwards Sapien valves and reported similar numbers of deaths during a maximum follow-up of 55 months of 1.6% (17/1,044 from 19 studies) and 1.2% (15/1,246 from 20 studies).[5, 8] The overall quality of the evidence was considered very low due to the inclusion of retrospective study designs and the indirectness.

One systematic review reported that 0.5% (5/1,044 from 19 studies) of patients died during the procedure.[8] Two reviews only reported deaths occurring in patients with infective endocarditis (IE) after the procedure, which occurred in 8.7% (6/69 cases) and 8% (18/219 cases).[6, 7] Analogically, the overall quality of the evidence is considered very low due to high risk of bias and indirectness.

Georgiev et al. 2020 compared the long-term outcomes in patients treated with percutaneous PVI with the Melody valve and SPVR in the German Heart Centre, Munich.[18] There were lower mortality rates following PVI (Melody valve) compared with SPVR at follow-up ranging from 8-84 months (OR = 0.55; 95% CI 0.21 to 1.46) based on very low-quality evidence.[18]

In their SR, Waqanivavalagi et al. 2020 evaluated clinical performance of decellularized heart valves versus standard tissue conduits.[19] The authors searched PubMed, Scopus, and Web of Science databases; and included 17 studies with 1,418 patients. Risk of bias was assessed using the Risk of Bias In Non-Randomized Studies of Interventions (ROBINS-I) tool. Most of the included studies were at a high risk of bias.[19] There were no differences in mortality rates between decellularised valves compared with standard tissue conduits (RR = 0.94; 95% CI 0.60 to 1.47). The quality of the evidence was considered very low due to high risk of bias and inconsistency (Table 4).

In their observational study, Nordmeyer et al. 2019 obtained and retrospectively analysed multicentre registry data after PPVR with the MM in a large-scale cohort of patients (N=845) with congenital heart disease.[20] The authors reported a procedure-related mortality rate of

0.6% at a median follow-up of 5.9 years. The overall quality of the evidence is considered very low due to high risk of bias and indirectness.

In their observational study, Sabate Rotes et al. 2014 evaluated prognostic factors for reintervention and death following SPVR in previously repaired tetralogy of Fallot among 278 patients.[22] The authors reported the highest survival rates for homografts, followed by porcine and pericardial (80.7%, 57.2% and 41.6% respectively at 5 years follow-up.[22] At 10 years follow-up, 73% of patients with homografts were alive, followed by 28.1% and 16.6% for porcine and pericardial respectively based on very low quality evidence.

Table 4: FAQ 2 – Mortality

Author	No. of studies (type of study)	Average follow-up time	PPVR	SPVR	Effect estimate (95% CIs), e.g., mean difference, risk ratio, odds ratio[b]	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event[a] Intervention/control group event rate (n/N)				
Periprocedural mortality (during admission or 30 days after PVR)							
Ribeiro 2020[2]	11 Cohort studies	Up to 30 days	2/1132 (0.2%)	60/4939 (1.2%)	OR = 0.56 (0.19 to 1.59)	Very low (high risk of bias and inconsistency)	No difference shown
Procedural mortality							
Chatterjee 2017[8]	19 Cohort studies	NR*	5/1,044 (0.5%)	NR	NR	Very low (high risk of bias and indirectness)	No comparison
Nordmeyer 2019 [20]	1 cohort study	Median = 5.9 years	5/845 (0.6%) for MM	NR	NR	Very low (high risk of bias and indirectness)	No comparison
In hospital mortality							
Zhou 2019[3]	3 Cohort studies	NR	1/654 (0.2%)	39/2339 (1.7%)	OR = 0.18 (0.03 to 0.98)	Very low (high risk of bias and imprecision)	Difference in favour of PPVR but data of very low quality
Mortality during follow-up							
Georgiev 2020[18]	Cohort study	8 to 84 months	7/241 (2.9%) for MM	11/215 (5.1%)^	OR = 0.55 (0.21 to 1.46)^^	Very low (high risk of bias and imprecision)	Difference in favour of MM but imprecise data of very low quality

Author	No. of studies (type of study)	Average follow-up time	PPVR	SPVR	Effect estimate (95% CIs), e.g., mean difference, risk ratio, odds ratio[b]	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event[a] Intervention/control group event rate (n/N)				
Ribeiro 2020[2]	6 Cohort studies	1.6 to 8.8 years	7/460 (1.5%)	28/1043 (2.7%)	OR = 0.78 (0.30 to 2.00)	Very low (high risk of bias and imprecision)	No difference shown
Zhou 2019[3]	11 Cohort studies	2.2 to 89 months	8/1284 (0.6%)	59/3080 (1.9%)	OR = 0.43 (0.22 to 0.87)	Very low (high risk of bias and imprecision)	Difference in favour of PPVR but data of very low quality
Ran 2019[5]	20 Cohort studies	1 to 55.2 months	15/1,246 (1.2%)	NR	NR	Very low (high risk of bias and indirectness)	No comparison
Survival							
Sabate Rotes 2014 [22]	1 cohort study	5 years	118/206 (57.2%) for porcine SPVR	21/26 (80.7%) for homograft	NR	Very low (high risk of bias and imprecision)	Difference in favour of homografts but data of very low quality
Sabate Rotes 2014 [22]	1 cohort study	5 years	15/36 (41.6%) for pericardial	118/206 (57.2%) for porcine SPVR	NR	Very low (high risk of bias and imprecision)	Difference in favour of porcine but data of very low quality
Sabate Rotes 2014 [22]	1 cohort study	10 years	58/206 (28.1%) for porcine SPVR	19/26 (73%) for homograft	NR	Very low (high risk of bias and imprecision)	Difference in favour of homografts but data of very low quality

Author	No. of studies (type of study)	Average follow-up time	PPVR	SPVR	Effect estimate (95% CIs), e.g., mean difference, risk ratio, odds ratio[b]	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event[a] Intervention/control group event rate (n/N)				
Sabate Rotes 2014 [22]	1 cohort study	10 years	6/36 (16.6%) for pericardial	19/26 (73%) for homograft	NR	Very low (high risk of bias and imprecision)	Difference in favour of homografts but data of very low quality
Mortality following PVR discharge							
Chatterjee 2017[8]	19 Cohort studies	NR*	17/1,044 (1.6%) 0.6 (95% CI 0.3 to 0.9) per 100 person-years	NR	NR	Very low (high risk of bias and indirectness)	No comparison
30-day mortality							
Zhou 2019[3]	6 Cohort studies	Up to 30 days	1/576 (0.2%)	8/574 (1.4%)	OR = 0.38 (0.11 to 1.33)	Very low (high risk of bias and imprecision)	No difference shown
McRae 2017[4]	58 Cohort studies	Up to 30 days	0.3% (range 0 to 1.6%) 18 studies	1% (range 0 to 10%) 40 studies	NR	Very low (high risk of bias and indirectness)	No comparison
Mortality (endpoint not specified)							
Abdelghani 2018[7]	69 case reports*	NR	6/69 (8.7%)	NR	NR	Very low (high risk of bias and indirectness)	No comparison
Lehner 2019[6]	219 cases**	3 to 108 months	18/219 (8%)	NR	NR	Very low (high risk of bias and indirectness)	No comparison

Author	No. of studies (type of study)	Average follow-up time	PPVR	SPVR	Effect estimate (95% CIs), e.g., mean difference, risk ratio, odds ratio[b]	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event[a] Intervention/control group event rate (n/N)				
Waqanivavalagi 2020 [19]	17 cohort and non-randomised studies	NR	64/1373 (4.6%) for decellularised	161/2629 (6.1%) for standard tissue conduits	RR = 0.94 (0.60 to 1.47)	Very low (high risk of bias and inconsistency)	No difference shown

[*] 69 patients with infective endocarditis after receiving Melody Valve; [**] 214 Melody valve and 5 Sapien valve patients with infective endocarditis
^ The majority of the surgically implanted valves were homografts (65%), followed by Hancock (27%), Contegra (5%), and other valves (3%).
^^ = own re-calculation, for more details, please refer to the appendix 2.
[a] The proportion with event is the overall number of deaths/number in group; [b] OR are the pooled values from the meta-analysis reported in the systematic review
CI = confidence interval; IE = infective endocarditis; MM = Medtronic Melody; NR = not reported; OR = odds ratio; PPVR = percutaneous pulmonary valve replacement; PVR = pulmonary valve replacement; RR = relative risk; SPVR = surgical pulmonary valve replacement

3.5 FAQ 3: WILL IT HELP MY SYMPTOMS?

There was a paucity of data for the impact of PPVR or SPVR on patient-reported symptoms.

Only the systematic review by McRae et al. 2017 provided any evidence for the alleviation of symptoms.[4] None of the PPVR studies included in the review evaluated specific symptoms such as breathlessness on exertion, fatigue, palpitations, or chest pain. Functional status was measured using the New York Heart Association (NYHA) functional class which was reported to significantly increase in all PPVR and SPVR studies, but no numerical results were reported in the included primary studies. Six PPVR and four SPVR studies with follow-up durations between one month and 3.4 years were included in the meta-analysis of exercise capacity. This showed a statistically significant increase in post-procedure peak oxygen consumption (VO_2 max; a quantitative value of endurance fitness) compared to levels before the procedure with PPVR (standardised mean difference [SMD] 0.343, 95% CI 0.103 to 0.584) which equates to an increase from 31.69 ml/kg/min pre-procedure to 34.76 ml/kg/min post-procedure (the greater result equates to better cardiac endurance) i.e. the clinical relevance is questionable. There was no evidence of an increase with SPVR (SMD -0.012, 95% CI -0174 to 0.150) which equates to an increase from 26.75 ml/kg/min pre-procedure to 27.15 ml/kg/min post-procedure. There was no direct comparison between PPVR and SPVR and this evidence was considered very low quality, results are shown in Table 5.

Table 5: FAQ 3 – Improvement in symptoms

Outcome	Author	No. of studies (type of study)	Average follow-up time	PPVR	SPVR	Effect estimate (95% CI) , e.g., mean difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
				SMD (95% CI) of change (post – pre) Pooled mean values				
Functional status (peak oxygen consumption)	McRae 2017[4]	10 Cohort studies	NR	0.343 (0.103 to 0.584) 31.69 (pre) 34.76 (post) ml/kg/min	-0.012 (-0.174 to 0.140) 26.75 (pre) 27.15 (post) ml/kg/min	NR	Very low (data of low quality and indirectness)	No difference shown
LVEF = left ventricular ejection fraction; NR = not reported; PPVR = percutaneous pulmonary valve replacement; SMD = standardised mean difference; SPVR = surgical pulmonary valve replacement								

3.6 FAQ 4: How long will treatment effect last? Will it help maintain remission of my disease?

Two systematic reviews and one observational study reported on significant (defined as moderate or severe) or recurrent pulmonary regurgitation following PVR. Details are provided in Table 6.

Ribeiro et al. 2020 included 18 observational studies directly comparing PPVR and SPVR which were judged to be at high risk of bias due to their study design.[2] Five studies were included in the meta-analysis of significant pulmonary regurgitation with follow-up times ranging from 1.9 to 7.4 years. PPVR reduced the odds of significant pulmonary regurgitation compared with SPVR (OR 0.21, 95% CI 0.06 to 0.69, five studies). The overall quality of the evidence was very low due to high risk of bias and imprecision.

Another systematic review by Zhou et al. 2019 also included observational studies directly comparing PPVR and SPVR.[3] The results also showed that recurrent pulmonary regurgitation was reduced with PPVR compared to SPVR (OR 0.17, 95% CI 0.07 to 0.42, 5 studies) during a follow-up period of up to 7.4 years. Although both reviews found a reduction in pulmonary regurgitation with PPVR compared to SPVR the quality of the evidence was very low due to the nature of observational study designs and imprecision.

Shahanavaz et al. 2020 sought to report short-term outcomes in a cohort of patients (N=774) who underwent PPVR with either a Sapien XT or S3 valve.[21] For this outcome, the authors reported no differences between stented bioprostheses and conduit homografts at a median follow-up of 12 months based on very low-quality evidence.[21]

Table 6: FAQ 4 – Recurrence of disease

Outcome	Author	No. of studies (type of study)	Average follow-up time	PPVR	SPVR	Effect estimate (95% CI), e.g., mean difference, risk ratio, odds ratio[b]	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
				Proportion with event[a] (n/N)				
Significant pulmonary regurgitation	Ribeiro 2020[2]	6 Cohort studies	1.9 to 7.4 years	2/481 (0.4%)	16/377 (4.2%)	OR = 0.21 (0.06 to 0.69)	Very low (high risk of bias and inconsistency)	Difference in favour of PPVR but data of very low quality
Recurrent pulmonary regurgitation	Zhou 2019[3]	5 Cohort studies	2.2 to 89 months	6/334 (1.8%)	32/312 (10.2%)	OR = 0.17 (0.07 to 0.42)	Very low (high risk of bias and inconsistency)	Difference in favour of PPVR but data of very low quality
Moderate or severe pulmonary regurgitation	Shahanavaz 2020 [21]	1 cohort study	Median = 12 months	3/194 (1.5%) for stented bioprostheses	2/183 (1.1%) for conduit homografts, stentless porcine, and other valved or nonvalved stentless conduits	OR = 1.42 (0.23 to 8.61)*	Very low (high risk of bias and imprecision)	No difference shown

CI = confidence interval; NR = not reported; OR = odds ratio; PPVR = percutaneous pulmonary valve replacement; SPVR = surgical pulmonary valve replacement.
[a] The proportion with event is the overall number of deaths/number in group
[b] OR are the pooled values from the meta-analysis reported in the systematic review. * = own calculations with RevMan 5.4.1-please refer to the appendix 2.

3.7 FAQ 5: How will treatment impact my quality of life?

There was a lack of quantitative evidence for the impact of PVR on quality of life.

The outcome was only reported in the systematic review by McCrae et al. 2017, however, no numerical results were provided.[4] The authors stated that five SPVR studies measured HRQoL using the 36-item short form questionnaire (SF-36) between six months and four years after surgery and many of the items showed significant improvement. Two SPVR studies measured health-related quality of life (HRQoL) in children using the Child Health Questionnaire Parent form and a 10-item short form specifically for children. Only one study measured HRQoL after PPVR using SF-36 six months after the procedure however no quantitative results were reported. No studies used disease-specific instruments.

3.8 FAQ 6: Will it impact my risk of having to go into the hospital?

Five systematic reviews reported on the numbers of patients requiring a re-intervention; and one observational study reported on freedom from reintervention.[2, 3, 7, 8, 19, 22]

Two of these directly compared PPVR with SPVR and included nine observational studies in the meta-analysis. [2,3] The first review found no evidence of a difference in reinterventions between PPVR and SPVR (OR 0.51, 95% CI 0.17 to 1.55) but this was very low-quality evidence due the observational study designs and high level of statistical heterogeneity between the individual study results.[2] The second review by Zhou et al. 2019 included observational studies directly comparing PPVR with SPVR.[3] This found no evidence of a difference between PPVR and SPVR in patients requiring reoperation (OR 2.19, 95% CI 0.62 to 7.76, five studies) but a reduction in 30-day hospital admissions with PPVR (OR 0.67, 95% CI 0.50 to 0.91, four studies). The overall quality of the evidence was very low.

The other two reviews only included studies evaluating PPVR. One found that 52% (35/69) of patients developing infective endocarditis needed reintervention.[7] The other included 19 observational studies and reported a reintervention rate of 4.4 (95% CI 3.0 to 5.9) per 100 person-years of follow-up and 5.5% (124/2,271) of patients requiring reintervention. Both reviews provided very low-quality evidence.

Waqanivavalagi et al. 2020 reported lower reoperation rates for decellularized heart valves compared with standard tissue conduits (RR=0.55; 95% CI 0.36 to 0.84).[19] The overall quality of the evidence was very low (Table 7).

Sabate Rotes et al. 2014 reported the highest freedom from reintervention for homografts, followed by porcine and pericardial (76.9%, 55.8% and 41.6% respectively at 5 years follow-up.[22] At 10 years follow-up 65.3% of patients with homografts were free from reintervention, followed by 23.7% and 22.2% for porcine SPVR and pericardial respectively based on very low-quality evidence.[22]

Table 7: FAQ 6 – Re-admission to hospital or reintervention

Author	No. of studies (type of study)	Average follow-up time	PPVR	SPVR	Effect estimate with (95% CIs), e.g., mean difference, risk ratio, odds ratio[b]	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event (n/N)[a]				
Reintervention							
Ribeiro 2020[2]	9 Cohort studies	1.9 to 7.4 years	23/902 (2.5%)	202/3,790 (5.3%)	OR = 0.51 (0.17 to 1.55)	Very low (high risk of bias and inconsistency)	No difference shown
Abdelghani 2018[7]	69 Case reports *	NR	35/69 (52%)	NR	NR	Very low (high risk of bias and indirectness)	No comparison
Chatterjee 2017[8]	19 Cohort studies	0.5 to 4.5 years	Rate 4.4 (95% CI 3.0 to 5.9) per 100 person-years 124/2271 (5.5%)	NR	NR	Very low (high risk of bias and indirectness)	No comparison
Freedom from reintervention							
Sabate Rotes 2014 [22]	1 cohort study	5 years	115/206 (55.8%) for porcine SPVR	20/26 (76.9%) for homograft	NR	Very low (high risk of bias and imprecision)	Difference in favour of homografts but data of very low quality
Sabate Rotes 2014 [22]	1 cohort study	5 years	15/36 (41.6%) for pericardial	115/206 (55.8%) for porcine SPVR	NR	Very low (high risk of bias and imprecision)	Difference in favour of porcine but data of very low quality
Sabate Rotes 2014 [22]	1 cohort study	10 years	49/206 (23.7%) for porcine SPVR	17/26 (65.3%) for homograft	NR	Very low (high risk of bias and imprecision)	Difference in favour of homografts but data of very low quality

Sabate Rotes 2014 [22]	1 cohort study	10 years	8/36 (22.2%) for pericardial	17/26 (65.3%) for homograft	NR	Very low (high risk of bias and imprecision)	Difference in favour of homografts but data of very low quality
30-days hospital readmission							
Zhou 2019[3]	4 Cohort studies	Up to 30 days	56/578 (9.67%)	420/2,121 (19.8%)	OR = 0.67 (0.50 to 0.91)	Very low (high risk of bias and imprecision)	Difference in favour of PPVR but data of very low quality
Reoperation							
Zhou 2019[3]	5 Cohort studies	2.2 to 89 months	22/534 (4.12%)	14/2,081 (0.67%)	OR = 2.19 (0.62 to 7.76)	Very low (high risk of bias and inconsistency)	No difference shown
Waqanivavalagi 2020 [19]	17 cohort and non-randomised studies	NR	66/1379 (4.7%) for decellularized valves	197/2661 (7.4%) for standard tissue conduits	RR = 0.55 (0.36 to 0.84)	Very low (high risk of bias and inconsistency)	Difference in favour of decellularized valves but data of very low quality

* 69 case reports of infective endocarditis after receipt of Melody valve and the deaths are reported from those

[a] The proportion with event is the overall number of deaths/number in group

[b] OR are the pooled values from the meta-analysis reported in the systematic review

CI = confidence interval; NR = not reported; OR = odds ratio; PPVR = percutaneous pulmonary valve replacement; RR = relative risk; SPVR = surgical pulmonary valve replacement.

3.9 FAQ 7: When will I recover?

There was no evidence for time to return to usual activity, however defined. Evidence for length of hospital stay was provided by the two reviews which directly compared PPVR and SPVR.[2, 3] Both reported a shorter duration of hospital stay with PPVR compared to SPVR with mean differences of -4.32 days (95% CI -5.33 to -3.31 days, 10 studies) and -4.38 days (95% CI -6.24 to -2.53 days, four studies) respectively. The quality of the evidence was very low in both studies due to the inclusion of observational studies and high levels of statistical heterogeneity in the meta-analysis.

Table 8: FAQ 7 – Length of hospital stay

Author	No. of studies (type of study)	Average follow-up time	PPVR	SPVR	Effect estimate (95% CIs)	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event event rate (n/N) Mean (SD)				
Ribeiro 2020[2]	10 cohort studies	NR	NR	NR	MD = -4.32 days (-5.33 to -3.31)	Very low (high risk of bias and inconsistency)	Difference in favour of PPVR but data of very low quality
Zhou 2019[3]	4 cohort studies	2.2 to 89 months	NR	NR	MD = -4.38 days (-6.24 to -2.53)	Very low (high risk of bias and inconsistency)	Difference in favour of PPVR but data of very low quality

CI = confidence interval; MD = mean difference; NR = not reported; PPVR = percutaneous pulmonary valve replacement; SPVR = surgical pulmonary valve replacement.

3.10 FAQs 8 and 9: What are the risks or side effects (specifically endocarditis)? Are there long-term negative effects of treatment to be expected?

Evidence for risks and side-effects was provided by the two reviews which directly compared PPVR and SPVR.[2, 3] Both reported increases in the occurrence of infective endocarditis with PPVR compared to SPVR with odds ratios (ORs) of 4.56 (95% CI 2.03 to 10.26, six studies) and 3.09 (95% CI 1.89 to 5.06, 10 studies) respectively. The quality of the evidence was very low in both studies due to the inclusion of observational studies and imprecision. Evidence for infective endocarditis induced by different types of valves was available from seven additional studies.[6, 7, 10, 11, 16-18] Findings were inconsistent, however pooled estimates from 47 cohort studies showed an increased risk of infective endocarditis for Medtronic Melody (MM) valve compared with Edwards Sapien (OR = 6.24; 95% CI 2.56 to 15.22) at follow-ups ranging from 20-59 months (Table 9). The quality of the evidence was low due to the inclusion of observational studies.[6]

Ribeiro 2020 also reported fewer procedure-related complications (definitions varied significantly) following PPVR compared with SPVR (OR 0.38, 95% CI 0.18 to 0.82, seven

studies).[2] For PPVR those complications included: unspecified cardiac complications (42%), non-intraoperative postprocedural events that impacted patient comfort, functional status, or length of hospitalization (8%), haemorrhage/hematoma (5%), respiratory complications (unspecified) (4%), other (unspecified) (4%), femoral pseudoaneurism (2%), femoral arteriovenous fistula (2%), stent fracture (2%), failure of transcatheter pulmonary valve deployment (2%), fever of unknown origin (2%), transient atrioventricular conduction block (2%), prestent embolization (1%), conduit perforation (1%), haemothorax, pneumothorax, or pleural effusion (1%), cardiopulmonary arrest with crushed Melody valve from chest compressions (1%), infection/fever (1%).[2] For SPVR those complications included: unspecified cardiac complications (33%), non-intraoperative postprocedural events that impacted patient comfort, functional status, or length of hospitalisation (25%), respiratory complications (unspecified) (24%), fever of unknown origin (23%), sternal wound infection (12%), other complications (unspecified) (10%), arrhythmia (7%), reoperation plus blood transfusion (7%), pacemaker implantation (7%), haemorrhage/hematoma (7%), infection/fever (4%), urgent reoperation because of bleeding (4%), haemothorax, pneumothorax, or pleural effusion (3%), death (2%), seizures (2%), bleeding or infection requiring mediastinal exploration (1%), cardiopulmonary arrest with residual neurologic deficits (1%), acute coronary injury (1%), recurrent pneumothorax (1%), hemi-diaphragmatic paralysis (1%).[2] Please note that for the same complications reported in multiple studies, e.g., pacemaker implantation, the highest estimate was derived from each study i.e., not pooled. The quality of the evidence was very low in this study due to the inclusion of observational studies and high levels of statistical heterogeneity in the meta-analysis.[2]

Gröning et al. 2019 investigated the incidence of IE in right ventricle-to-pulmonary artery conduits implanted at a Danish tertiary centre.[16] There were similar rates of IE for both homografts and Contegra (2% and 5%) at follow-ups ranging from 1 to 5 years. However, MM was associated with greater risk of IE when compared with homografts (HR = 11.89; 95% CI 2.91 to 48.48) at follow-ups ranging from 1 to 5 years. The quality of the evidence was very low in this study due to the inclusion of observational studies and imprecision (Table 9).

McElhinney et al. 2018 evaluated rates and potential risk factors for IE after transcatheter PVR in the prospective Melody valve trials.[17] There were no differences between homografts and Contegra (12.1% versus 7.6%; OR = 1.65; 95% CI 0.21 to 13.22).[17] Analogically, the quality of the evidence was very low in this study due to the inclusion of observational studies and imprecision (Table 9).

Georgiev et al. 2020 reported lower rates of IE following SPVR compared with percutaneous PVR (Melody valve) at follow-up ranging from 8-84 months (OR = 2.81; 95% CI 1.10 to 7.22) based on very low-quality evidence.[18]

Mery et al. 2016 evaluated risk factors for developing endocarditis and reintervention in patients undergoing right ventricle conduit placement with homografts, aortic homografts, bovine jugular grafts and porcine heterografts.[23] The authors reported lower rates of IE

following homografts compared with bovine jugular or heterografts (OR=0.16; 95% CI 0.05 to 0.50; and OR=0.26; 95% CI 0.07 to 0.98 respectively) based on very low-quality evidence.[23]

Shahanavaz et al. 2020 reported no differences between stented bioprostheses and conduit homografts in the number of serious procedural adverse event at a median follow-up of 12 months (OR = 0.60; 95% CI 0.28 to 1.29) based on very low-quality evidence.[21]

Table 9: FAQs 8 & 9 – Short and long-terms risks or side-effects of interventions

Author	No. of studies (type of study)	Average follow-up time	Intervention	Control	Effect estimate with 95% CIs, e.g., mean/ median difference, risk ratio, odds ratio [b]	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event [a] Intervention/control group event rate (n/N)				
Infective endocarditis							
Chatterjee 2017[8]	19 Cohort studies	NR*	1.4 (95% CI 0.9 to 2.0) per 100 person-years (PPVR)	NR (SPVR)	NR	Very low (high risk of bias, and imprecision)	No comparison
Ribeiro 2020[2]	10 Cohort studies	NR	46/793 (5.8%) (PPVR)	41/1,545 (2.7%) (SPVR)	OR = 3.09 (1.89 to 5.06)	Very low (high risk of bias and imprecision)	Difference in favour of SPVR but data of very low quality
Zhou 2019[3]	6 Cohort studies	NR	28/543 (5.2%) (PPVR)	7/594 (1.2%) (SPVR)	OR = 4.56 (2.03 to 10.26)	Very low (high risk of bias and imprecision)	Difference in favour of SPVR but data of very low quality
Lehner 2019[6]	47 Cohort studies	Mean range: 23-35 months	214/3616 (5.9%) for MM	5/501 (0.99%) for ESA	OR = 6.24 (2.56 to 15.22)**	Low (high risk of bias)	Difference in favour of ESA but data of low quality
Abdelghani 2018[7]	9 Cohort studies	Median: 31 months (range: 20-59)	93/851 (10.92%; range: 3.2-25%) for MM	NR	NR	Very low (high risk of bias and imprecision)	No comparison
Botrel 2013[10]	15 Cohort and case control studies	Median range: 4-30 months	13/644 (2.01%) for MM	0/34 (0%) for ESA	OR = 1.48 (0.09 to 25.33)**	Very low (high risk of bias and imprecision)	No difference shown

Author	No. of studies (type of study)	Average follow-up time	Intervention	Control	Effect estimate with 95% CIs, e.g., mean/ median difference, risk ratio, odds ratio [b]	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event [a] Intervention/control group event rate (n/N)				
Sharma 2017[11]	20 Cohort studies	Range: 9.8-105.6 months	51/814 (6.2%) for MM	60/840 (7.1%) for Contegra	OR = 0.87 (0.59 to 1.28)**	Very low (high risk of bias and imprecision)	No difference shown
Sharma 2017[11]	35 Cohort studies	Range: 3-165.6 months	61/4671 (1.3%) for homografts	9/619 (1.4%) for bioprosthetic	OR = 0.90 (0.44 to 1.82)**	Very low (high risk of bias and imprecision)	No difference shown
Georgiev 2020[18]	Cohort study	8 to 84 months	18/241 (7.4%) for MM	6/215 (2.7%) for SPVR^	OR = 2.81 (1.10 to 7.22)**	Very low (high risk of bias and imprecision)	Difference in favour of SPVR but data of very low quality
McElhinney 2018[17]	Cohort study	Median = 60.1 patient years	27/223 (12.1%) for homografts^^	1/13 (7.6%) for Contegra^^	OR = 1.65 (0.21 to 13.22)**	Very low (high risk of bias and imprecision)	No difference shown
Gröning 2019[16]	Cohort study	1 to 5 years	5/259 (2%) for homografts	5/109 (5%) for Contegra	OR = 0.41 (0.12 to 1.44)**	Very low (high risk of bias and imprecision)	No difference shown
Gröning 2019[16]	Cohort study	1 to 5 years	7/64 (11%) for MM	5/259 (2%) for homografts	HR = 11.89 (2.91 to 48.48)	Very low (high risk of bias and imprecision)	Difference in favour of homografts but data of very low quality
Nordmeyer 2019 [20]	1 cohort study	6 years	11.4% (95% CI 10.3 to 12.5) for MM	NR	NR	Very low (high risk of bias and indirectness)	No comparison

Author	No. of studies (type of study)	Average follow-up time	Intervention	Control	Effect estimate with 95% CIs, e.g., mean/ median difference, risk ratio, odds ratio [b]	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event [a] Intervention/control group event rate (n/N)				
Nordmeyer 2019 [20]	1 cohort study	8 years	16.2% (95% CI 14.6 to 18.1) for MM	NR	NR	Very low (high risk of bias and indirectness)	No comparison
Mery 2016 [23]	1 cohort study	Median = 5 years	4/410 (0.97%) for homograft	14/245 (5.7%) for bovine jugular	OR=0.16 (0.05 to 0.50)**	Very low (high risk of bias and imprecision)	Difference in favour of homografts but data of very low quality
Mery 2016 [23]	1 cohort study	Median = 5 years	5/137 (3.6%) for heterograft	4/410 (0.97%) for homograft	OR=0.26 (0.07 to 0.98)**	Very low (high risk of bias and imprecision)	Difference in favour of homografts but data of very low quality
Procedure-related complications							
Ribeiro 2020[2]	7 Cohort studies	NR	120/726 (16.5%)	643/1,558 (41.3%)	OR = 0.38 (0.18 to 0.82)	Very low (high risk of bias and inconsistency)	Difference in favour of PPVR but data of very low quality
Any serious procedural adverse event							
Shahanavaz 2020 [21]	1 cohort study	Median = 12 months	12/164 (7.3%) for stented bioprostheses	19/164 (12%) for conduit homografts, stentless porcine, and other valved or nonvalved	OR = 0.60 (0.28 to 1.29)**	Very low (high risk of bias and imprecision)	No difference shown

Author	No. of studies (type of study)	Average follow-up time	Intervention	Control	Effect estimate with 95% CIs, e.g., mean/ median difference, risk ratio, odds ratio [b]	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event [a] Intervention/control group event rate (n/N)				
				stentless conduits			

* = follow-up only reported as patient years
** = own re-calculation, for more details, please refer to the appendix 2.
^ = The majority of the surgically implanted valves were homografts (65%), followed by Hancock (27%), Contegra (5%), and other valves (3%).
^^ = estimates for transcatheter pulmonary valve–related endocarditis
[a] The proportion with event is the overall number of deaths/number in group
[b] OR are the pooled values from the meta-analysis reported in the systematic review CI = confidence interval; ESA = Edwards SAPIEN; HR = hazard ratio; MM = Medtronic Melody; NR = not reported; OR = odds ratio; PPVR = percutaneous pulmonary valve replacement; SPVR = surgical pulmonary valve replacement

3.11 FAQ 10: How long will the graft last?

Evidence for structural valve deterioration (SVD) was provided by the two reviews and two cohort studies which compared different types of valves i.e., homograft, bioprosthesis, bovine pericardial, Contegra, Edwards Prima, Edwards porcine conduit, MF, MM, Hancock II, Perimount and Toronto.[12-15] The two SRs only provided percentage values so no pooled effect estimates were available.[12, 13] Follow-ups raged from 1 month to 10 years (Table 10). For example, at three years, failure rates ranged from 0% for Edwards porcine conduit to 20% for Edwards Prima.[13] At five years, these rates were 40% for homografts and 11% for bovine pericardial.[13] At ten years, these rates were as high as range: 25-60% for homografts or 50% for Hancock II compared with 22% for bovine pericardial or 20% for Toronto.[13] In their cohort study, Cocomello et al. 2019 compared long-term results after PVR with pulmonary homografts versus bioprosthesis using data from a 20-year single-centre. The authors reported a lower rate of SVD for homografts compared with bioprostheses (13.3% versus 18.6%; OR = 0.67; 95% CI 0.30 to 1.49) at follow-ups ranging from 2 to 13 years.[14] Bell et al. 2018 compared the long-term performance of pulmonary homografts and stented bioprosthetic valves in patients aged 10–20 years. The authors also reported a lower rate of SVD for homografts compared with bioprostheses (15.2% versus 15.7%; OR = 0.96; 95% CI 0.41 to 2.26) at median follow-ups of 9.11 years for homografts and 3.02 years for bioprosthesis respectively.[15] The quality of the evidence was very low in both studies due to the inclusion of observational studies and imprecision (Table 10).

Table 10: FAQ 10– Structural valve deterioration

Author	No. of studies (type of study)	Average follow-up time	Intervention	Control	Effect estimate with 95% CIs, e.g., mean/ median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event Intervention/control group event rate (n/N)				
Structural valve deterioration							
Van den Eynde 2020[12]	6 Cohort studies	1-87.6 months	12/156 7.5% for MF	NR	NR	Very low (high risk of bias, and imprecision)	No comparison
Dunne 2015[13]	19 Cohort studies	3 years	(12%) for homografts	NR	NR	Very low (high risk of bias, and imprecision)	No comparison
Dunne 2015[13]	19 Cohort studies	3 years	(20%) for Edwards Prima	NR	NR	Very low (high risk of bias, and imprecision)	No comparison
Dunne 2015[13]	19 Cohort studies	3 years	0% Edwards porcine conduit	NR	NR	Very low (high risk of bias, and imprecision)	No comparison
Dunne 2015[13]	19 Cohort studies	3 years	7.1-16.4% for MF	NR	NR	Very low (high risk of bias, and imprecision)	No comparison
Dunne 2015[13]	19 Cohort studies	3 years	2-10% for MM	NR	NR	Very low (high risk of bias, and imprecision)	No comparison
Dunne 2015[13]	19 Cohort studies	3 years	10.5% for Toronto	NR	NR	Very low (high risk of bias, and imprecision)	No comparison

Author	No. of studies (type of study)	Average follow-up time	Intervention	Control	Effect estimate with 95% CIs, e.g., mean/ median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event Intervention/control group event rate (n/N)				
Dunne 2015[13]	19 Cohort studies	5 years	40% for homografts	NR	NR	Very low (high risk of bias, and imprecision)	No comparison
Dunne 2015[13]	19 Cohort studies	5 years	11% for bovine pericardial	NR	NR	Very low (high risk of bias, and imprecision)	No comparison
Dunne 2015[13]	19 Cohort studies	5 years	20-27% for Contegra	NR	NR	Very low (high risk of bias, and imprecision)	No comparison
Dunne 2015[13]	19 Cohort studies	5 years	4-17% for Hancock II	NR	NR	Very low (high risk of bias, and imprecision)	No comparison
Dunne 2015[13]	19 Cohort studies	5 years	11-26% for Perimount	NR	NR	Very low (high risk of bias, and imprecision)	No comparison
Dunne 2015[13]	19 Cohort studies	10 years	25-60% for homografts	NR	NR	Very low (high risk of bias, and imprecision)	No comparison
Dunne 2015[13]	19 Cohort studies	10 years	22% for bovine pericardial	NR	NR	Very low (high risk of bias, and imprecision)	No comparison
Dunne 2015[13]	19 Cohort studies	10 years	50% for Hancock II	NR	NR	Very low (high risk of bias, and imprecision)	No comparison

Author	No. of studies (type of study)	Average follow-up time	Intervention	Control	Effect estimate with 95% CIs, e.g., mean/ median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event Intervention/control group event rate (n/N)				
Dunne 2015[13]	19 Cohort studies	10 years	20% for Toronto	NR	NR	Very low (high risk of bias, and imprecision)	No comparison
Bell 2018[15]	Cohort study	Median = 9.11 for homografts and 3.02 for bioprosthesis	20/131 (15.2%) for homografts	9/57 (15.7%) for bioprosthesis	OR = 0.96 (0.41 to 2.26)*	Very low (high risk of bias, and imprecision)	Difference in favour of homografts but imprecise data of very low quality
Cocomello 2019 [14]	Cohort study	Median (IQR) 10 (5–13) for homografts and 4 (2–7) for bioprosthesis	10/75 (13.3%) for homografts	25/134 (18.6%) for bioprosthesis	OR = 0.67 (0.30 to 1.49)*	Very low (high risk of bias, and imprecision)	Difference in favour of homografts but imprecise data of very low quality
* = own re-calculation, for more details, please refer to the appendix 2. IQR = interquartile range; MF = Medtronic Freestyle; MM = Medtronic Melody; NR = not reported.							

4. DISCUSSION

4.1 SUMMARY OF MAIN FINDINGS

In general terms, the quantity and quality of the available evidence is suboptimal; twelve SRs and one CPG of observational evidence and five observational studies met the eligibility criteria. No RCTs directly comparing PPVR and SPVR were found.

Specifically, however, for FAQ 2 very low certainty evidence suggests that when compared with SPVR, PPVR may reduce in hospital mortality or mortality during follow-up (range: 2.2 to 89 months).[3, 18] Very low certainty evidence (observational study designs and imprecision) shows no difference between SPVR and PPVR for reducing 30-days mortality.[3] Similarly, very low certainty evidence shows no difference between SPVR and PPVR for mortality during follow-up (range: 1.6 to 8.8 years) and periprocedural mortality (during admission or 30 days after PVR).[2] There were no differences in mortality rates (where endpoints were not specified) between decellularised valves compared with standard tissue conduits.[19] However, the highest survival rates for homografts have been reported, followed by porcine and pericardial at 5 and 10 years follow-up.[22]

For FAQ 3, very low certainty evidence shows no difference between SPVR and PPVR for post-procedural peak oxygen consumption compared to levels before the procedure.[4]

For FAQ 4, based on very low certainty evidence, the findings consistently showed that compared with SPVR, PPVR reduced the odds of significant pulmonary regurgitation as well as recurrent pulmonary regurgitation.[2, 3] For this outcome, no differences between stented bioprostheses and conduit homografts were reported at a median follow-up of 12 months.[21]

For FAQ 5, none of the studies reported quantitative evidence for the impact of PVR on quality of life. Narrative findings only are available; and improvements were found following both procedures SPVR and PPVR.[4]

For FAQ 6, based on very low certainty evidence, the findings showed that compared with SPVR, PPVR reduced the odds of 30-days hospital readmission.[3] However very low certainty evidence shows no difference between SPVR and PPVR for reintervention or reoperation.[2, 3] Very low certainty evidence shows lower reoperation rates for decellularized heart valves compared with standard tissue conduits.[19] The highest freedom from reintervention rates were reported for homografts, followed by porcine and pericardial at 5 and 10 years follow-ups.[22]

For FAQ 7, based on very low certainty evidence, the findings consistently showed that compared with SPVR, PPVR reduced the length of hospital stay.[2, 3]

For FAQs 8 and 9 the findings were inconsistent. For instance, very low certainty evidence suggests that PPVR increases the risk of infective endocarditis compared to SPVR.[2, 3, 16, 18] As per different types of valves, our analyses showed an increased risk of infective endocarditis for Medtronic Melody valve (5.9%) compared with Edwards Sapien (0.99%) at follow-ups ranging from 20-59 months, based on low quality evidence.[6] Very low certainty evidence shows no differences between homografts and Contegra in IE.[17] Furthermore, based on very low certainty evidence, the findings showed that compared with SPVR, PPVR had lower odds of procedure-related complications. There were lower rates of IE following homografts compared with bovine jugular or heterografts based on very low-quality evidence.[23] Though, there were no differences between stented bioprostheses and conduit homografts for the number of serious procedural AEs at a median follow-up of 12 months.[21]

For FAQ 10 the findings were often incomparable. For example, very low certainty evidence suggests that at Toronto valves outperformed homografts at 10 years follow up whereas Edwards porcine conduit outperformed Edwards Prima at 3 years follow-up.[13] However, two studies consistently showed lower rates of SVD following homografts compared with bioprosthesis based on very low certainty evidence.[14, 15]

4.2 Strength, limitations and uncertainties

This report was developed using evidence from SRs and CPG. Its strengths include comprehensive literature searches without language or date restrictions, inclusion of the highest certainty evidence as well as coverage of a wide range of FAQs. However, some limitations or/and uncertainties should be taken into consideration. Firstly, up to 20% of patients in two SRs included children and adolescents with mean or median age lower than 14.[2, 3] However, by removing these two SRs we would not be able to answer the respective FAQ making the report less comprehensive. Secondly, the total with an event and total number of patients are added up across all studies hence they do not correspond to the presented ORs from the meta-analyses (even though in theory with highly variable weights given to studies in the meta-analyses, these results could be possible). Thirdly, for FAQ 5, only qualitative data were available; and there was a paucity of data for FAQ 3 i.e., patient-reported symptoms such as breathlessness on exertion, fatigue, palpitations, or chest pain. Mortality and the risk of re-admission to hospital or reintervention were the clinical areas where most of the evidence was found. Some inconsistencies in the results were also observed for risks and side effects i.e., either favouring SPVR versus PPVR for infective endocarditis or favouring PPVR for procedure-related complications. In contrast, the findings were consistent in favouring PPVR versus SPVR for pulmonary regurgitation and length of hospital stay. One of the main limitations is observational nature of the evidence as all studies were cohort studies, case-series or case-control studies. As a result, all the outcomes were

based on low or very low certainty evidence. Some results were downgraded for inconsistency due to high levels of high statistical heterogeneity in the pooled analyses; others due to imprecision.

5. REFERENCES

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APPENDIX 1: SEARCH STRATEGIES

Systematic reviews and guideline search results

Database	Date searched	Dates	2020 Results	2021 Results
CDSR	13.4.21	2016-2021/04/Iss4	16	156
DARE	14.4.21	NA*	13	0
HTA	14.4.21	2016 -2018/03/31	15	20
INAHTA	14.4.21	2016- 2021/04/14	14	46
KSR Evidence	14.4.21	2016-2021/04/14	84	268
Epistemonikos	15.4.21	2016-2021/04/15	133	239
NICE Guidance	13.4.21	2016- 2021/04/13	3	2
ECRI Guidelines	15.4.21	Up to 2021/04/15	3	31
NICE/NHS Evidence	14.4.21	2016-2021/04/14	52	109
TRiP	14.4.21	2016-2021/04/14	128	30
GIN	13.4.21	Up to 2021/04/13	3	19
Total			**464**	**920**
Total after de-duplication			**202**	**588**

*DARE is now an archival resource and was last updated in March 2015

SEARCH STRATEGIES

Cochrane Database of Systematic Reviews (CDSR)(Wiley): up to 2021/04/Iss4
Searched 13.4.21

#1 MeSH descriptor: [Pulmonary Valve] this term only 14
#2 (Pulmonary or pulmonic) NEAR/3 (valve* or valva or cusp or valvula) 420
#3 (TPVR or PPVR or PVR or SPVR or PVI):ti,ab 2292
#4 "lung valve*" or "lung artery valve*" or "lung trunk valve*" 0
#5 "truncus arteriosus" or "valva trunci pulmonalis" 16
#6 "pulmonary regurgitation" or "pulmonary atresia" or "pulmonary stenosis" 91
#7 "right ventricular outflow tract" or RVOT 158
#8 "tetralogy of Fallot" 254
#9 "Ross procedure" 18
#10 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 3045

#11 MeSH descriptor: [Allografts] explode all trees 200
#12 MeSH descriptor: [Heterografts] explode all trees 65
#13 ((allogeneic or homologous or heterologous or heterogenous or xenogeneic or Decellularized or decellularised or porcine or pig or cow or Melody or Sapien or bovine or Contect or allo) NEAR/3 (graft* or transplant* or valve* or implant*)):ti,ab 2803
#14 (allograft* or homograft* or Xenograft* or conduit or alloplastic or allotransplant* or homotransplant* or heterotransplant* or heterograft* or xenotransplant*):ti,ab 6307
#15 ("SAPIEN XT Pulmonic" or Edwards Sapien or "CE PERIMOUNT" or "CE Magna Magna Ease" or "Mitroflow LXE" or Contegra or "Venus p-valve" or "Alterra Adaptive Prestent" or "Pulsta valve" or Hancock or “Melody TPV” or "Medtronic Freestyle" or "Medtronic Harmony" or "Melody valve" or "Melody transcatheter pulmonary valve"):ti,ab 148
#16 #11 or #12 or #13 or #14 or #15 9030
#17 #10 or #16 with Cochrane Library publication date Between Jan 2016 and Apr 2021, in Cochrane Reviews 156

Health Technology Assessment (HTA) Database (CRD): up to 2018/03/31
https://www.crd.york.ac.uk/CRDWeb/
Date searched 14.4.21

1 MeSH DESCRIPTOR Pulmonary Valve EXPLODE ALL TREES 7 Delete
2 (Pulmonary or pulmonic) 2755 Delete
3 (valve* or valva or cusp or valvula) 549 Delete
4 #2 AND #3 51 Delete
5 (TPVR or PPVR or PVR or SPVR or PVI) 31 Delete
6 ("lung valve*" or "lung artery valve*" or "lung trunk valve*") 0 Delete
7 ("truncus arteriosus" or "valva trunci pulmonalis") 2 Delete
8 ("pulmonary regurgitation" or "pulmonary atresia" or "pulmonary stenosis") 4 Delete
9 ("right ventricular outflow tract" or RVOT) 7 Delete
10 ("tetralogy of Fallot") 11 Delete
11 ("Ross procedure") 4 Delete
12 #1 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 96 Delete
13 MeSH DESCRIPTOR Allografts EXPLODE ALL TREES 21 Delete
14 MeSH DESCRIPTOR Heterografts EXPLODE ALL TREES 0 Delete
15 (allogeneic or homologous or heterologous or heterogenous or xenogeneic or Decellularized or decellularised or porcine or pig or cow or Melody or Sapien or bovine or Contect or allo) 500 Delete
16 ((graft* or transplant* or valve* or implant*)) 6189 Delete
17 #15 AND #16 273 Delete
18 (allograft* or homograft* or Xenograft* or conduit or alloplastic or allotransplant* or homotransplant* or heterotransplant* or heterograft* or xenotransplant*) 241 Delete
19 ("SAPIEN XT Pulmonic" or Edwards Sapien or "CE PERIMOUNT" or "CE Magna Magna Ease" or "Mitroflow LXE" or Contegra) 6 Delete

20 ("Venus p-valve" or "Alterra Adaptive Prestent" or "Pulsta valve" or Hancock or "Melody TPV")45 Delete
21 ("Medtronic Freestyle" or "Medtronic Harmony" or "Melody valve" or "Melody transcatheter pulmonary valve") 0 Delete
22 #12 OR #13 OR #14 OR #17 OR #18 OR #19 OR #20 OR #21 587 Delete
23 (#22) FROM 2016 TO 2021 20 Delete

HTA retrieved 20 records

INAHTA International HTA database (https://database.inahta.org/): up to 2021/04/14
Date searched 14.4.21

("Pulmonary Valve"[mh]) OR ("pulmonary valve*" or "pulmonic valve*" or "pulmonary trunk valve*") OR ("lung valve*" or "lung artery valve*" or "lung trunk valve*") OR ("truncus arteriosus" or "valva trunci pulmonalis") OR ("pulmonary regurgitation" or "pulmonary atresia" or "pulmonary stenosis") OR ("right ventricular outflow tract") OR ("tetralogy of Fallot") OR ("Ross procedure") OR (graft OR grafts OR allograft OR homograft OR Xenograft OR heterograft OR alloplastic OR allotransplant OR homotransplant OR heterotransplant OR "SAPIEN XT Pulmonic" OR "Edwards Sapien" OR "CE PERIMOUNT" OR "CE Magna Magna Ease" OR "Mitroflow LXE" OR Contegra OR "Venus p-valve" OR "Alterra Adaptive Prestent" OR "Pulsta valve" OR Hancock OR "Melody TPV" OR "Medtronic Freestyle" OR "Medtronic Harmony" OR "Melody valve") FROM 2016 TO 2021

INAHTA retrieved 46 records

KSR Evidence (Internet) (https://ksrevidence.com/): up to 2021/04/14
Searched 14.4.21

1 Pulmonary or pulmonic in All text 5106 results

2 valve* or valva or cusp or valvula in All text 1205 results

3 #1 and #2 in All text 116 results

4 "lung valve*" or "lung artery valve*" or "lung trunk valve*" in All text 0 results

5 "truncus arteriosus" or "valva trunci pulmonalis" in All text 3 results

6 "pulmonary regurgitation" or "pulmonary atresia" or "pulmonary stenosis" in All text 15 results

7 "right ventricular outflow tract" or RVOT in All text 20 results

8 "Ross procedure" in All text 8 results

9 "tetralogy of Fallot" in All text 40 results

10 allogeneic or homologous or heterologous or heterogenous or xenogeneic or Decellularized or decellularised or porcine or pig or cow or Melody or Sapien or bovine or Contect or allo in Title or Abstract 838 results

11 graft* or transplant* or valve* or implant* in All text 9804 results

12 #10 and #11 in All text 302 results

13 allograft* or homograft* or Xenograft* or alloplastic or allotransplant* or homotransplant* or heterotransplant* or heterograft* or xenotransplant* in Title or Abstract 523 results

14 #12 or #13 in All text 789 results

15 cardiac or myocardial or heart or pulmon* or valve* or lung* in All text 22315 results

16 #14 and #15 in All text 110 results

17 "SAPIEN XT Pulmonic" or "Edwards Sapien" or "CE PERIMOUNT" or "CE Magna Magna Ease" or "Mitroflow LXE" or Contegra or "Venus p-valve" or "Alterra Adaptive Prestent" or "Pulsta valve" or Hancock or "Melody TPV" or "Medtronic Freestyle" or "Medtronic Harmony" or "Melody valve" or "Melody transcatheter pulmonary valve" in All text 68 results

18 #3 or #4 or #5 or #6 or #7 or #8 or #9 or #16 or #17 in All text 268 results

Filtered by: PUBLICATION DATE 2021, 2020, 2019, 2018, 2017, 2016

Epistemonikos (https://www.epistemonikos.org/en/): up to 2021/04/15
Searched 15.4.21

Limits: date range: 2016-2021 Publication type: Systematic Review Cochrane Review: No

Keywords	**Results**
(title:(Pulmonary OR pulmonic) OR abstract:(Pulmonary OR pulmonic)) AND (title:(valve* OR valva OR cusp OR valvula) OR abstract:(valve* OR valva OR cusp OR valvula))	81
(title:("lung valve*" OR "lung artery valve*" OR "lung trunk valve*" OR "truncus arteriosus" OR "valva trunci pulmonalis" OR	71

"pulmonary regurgitation" OR "pulmonary atresia" OR "pulmonary stenosis" OR "right ventricular outflow tract" OR RVOT OR "tetralogy of Fallot" OR "Ross procedure") OR abstract:("lung valve*" OR "lung artery valve*" OR "lung trunk valve*" OR "truncus arteriosus" OR "valva trunci pulmonalis" OR "pulmonary regurgitation" OR "pulmonary atresia" OR "pulmonary stenosis" OR "right ventricular outflow tract" OR RVOT OR "tetralogy of Fallot" OR "Ross procedure"))	
(title:(allogeneic OR homologous OR heterologous OR heterogenous OR xenogeneic OR Decellularized OR decellularised OR porcine OR pig OR cow OR Melody OR Sapien OR bovine OR Contect OR allo) OR abstract:(allogeneic OR homologous OR heterologous OR heterogenous OR xenogeneic OR Decellularized OR decellularised OR porcine OR pig OR cow OR Melody OR Sapien OR bovine OR Contect OR allo)) AND (title:(graft* OR transplant* OR valve* OR implant*) OR abstract:(graft* OR transplant* OR valve* OR implant*)) AND (title:(cardiac OR myocardial OR heart OR pulmon* OR valve* OR lung*) OR abstract:(cardiac OR myocardial OR heart OR pulmon* OR valve* OR lung*))	49
(title:(allograft* OR homograft* OR Xenograft* OR alloplastic OR allotransplant* OR homotransplant* OR heterotransplant* OR heterograft* OR xenotransplant*) OR abstract:(allograft* OR homograft* OR Xenograft* OR alloplastic OR allotransplant* OR homotransplant* OR heterotransplant* OR heterograft* OR xenotransplant*)) AND (title:(cardiac OR myocardial OR heart OR pulmon* OR valve* OR lung*) OR	60

abstract:(cardiac OR myocardial OR heart OR pulmon* OR valve* OR lung*))	
(title:("SAPIEN XT Pulmonic" OR "Edwards Sapien" OR "CE PERIMOUNT" OR "CE Magna Magna Ease" OR "Mitroflow LXE" OR Contegra OR "Venus p-valve" OR "Alterra Adaptive Prestent" OR "Pulsta valve" OR Hancock OR "Melody TPV" OR "Medtronic Freestyle" OR "Medtronic Harmony" OR "Melody valve" OR "Melody transcatheter pulmonary valve") OR abstract:("SAPIEN XT Pulmonic" OR "Edwards Sapien" OR "CE PERIMOUNT" OR "CE Magna Magna Ease" OR "Mitroflow LXE" OR Contegra OR "Venus p-valve" OR "Alterra Adaptive Prestent" OR "Pulsta valve" OR Hancock OR "Melody TPV" OR "Medtronic Freestyle" OR "Medtronic Harmony" OR "Melody valve" OR "Melody transcatheter pulmonary valve"))	24
Total	**285**
Total without dupes	**239**

National Institute for Health and Care Excellence (NICE) Guidance (Internet)(https://www.nice.org.uk/guidance): up to 2021/04/13
Date searched 13.4.21

Limits -
Document type: Guidance (limited 2016-C)

Search terms	**Records**
Pulmonary valve	0
Lung valve	0
truncus	0

trunci	0
right ventricular outflow tract	0
Fallot	0
Ross procedure	0
graft	2
grafts	0(1)
allograft	0(1)
homograft	0
Xenograft	0
Total before deduplication	**4**
Total after deduplication	**2**

ECRI (Internet)(https://guidelines.ecri.org/): up to 2021/04/15
Date searched 15.4.21

Search terms	**Records**
Pulmonary valve	4
Lung valve	2
truncus	0
trunci	0
right ventricular outflow tract	0
Fallot	0
Ross procedure	1
graft	25
grafts	25
allograft	8
homograft	0

Xenograft	3
Total before deduplication	**68**
Total after deduplication	**31**

NICE/NHS Evidence (Internet) (https://www.evidence.nhs.uk): up to 2021/04/14
Date searched 14/4/21

Limits: Guidance & SRs (2016-C)

Search terms	**Records**
“Pulmonary valve” or "Lung valve" or truncus or trunci or "right ventricular outflow tract" or "tetralogy of fallot" or "Ross procedure"	48
("SAPIEN XT Pulmonic" or Edwards Sapien or "CE PERIMOUNT" or "CE Magna Magna Ease" or "Mitroflow LXE" or Contegra or "Venus p-valve" or "Alterra Adaptive Prestent" or "Pulsta valve" or Hancock or “Melody TPV” or "Medtronic Freestyle" or "Medtronic Harmony" or "Melody valve" or "Melody transcatheter pulmonary valve")	67
Total before deduplication	**115**
Total after deduplication	**109**

Trip Database (https://www.tripdatabase.com/): up to 2021/04/14
Date searched 14.4.21

Document type: Guidelines

Search terms	**hits**
"Pulmonary valve" OR "Lung valve" OR truncus OR trunci OR "right ventricular	23*

outflow tract" OR Fallot OR "Ross procedure" 2019-C	
((Title: graft OR grafts OR allograft OR homograft OR Xenograft OR heterograft OR alloplastic OR allotransplant OR homotransplant OR heterotransplant OR "SAPIEN XT Pulmonic" OR "Edwards Sapien" OR "CE PERIMOUNT" OR "CE Magna Magna Ease" OR "Mitroflow LXE" OR Contegra OR "Venus p-valve" OR "Alterra Adaptive Prestent" OR "Pulsta valve" OR Hancock OR "Melody TPV" OR "Medtronic Freestyle" OR "Medtronic Harmony" OR "Melody valve") from:2016	7
Total	**30**

*This line is an update of the search run in 2020, hence the 2019 date limit

Guidelines International Network (G-I-N) (https://guidelines.ebmportal.com/): up to 2021/4/13
Date searched 13.4.21

Search terms	**Records**
valve	12
truncus	1
trunci	0
right ventricular outflow tract	0
fallot	1
Ross procedure	0
graft	3
allograft	1
homograft	0

Xenograft	1
Total before deduplication	**19**

APPENDIX 2: OWN RE-CALCULATIONS WITH REVIEW MANAGER 5.4.1

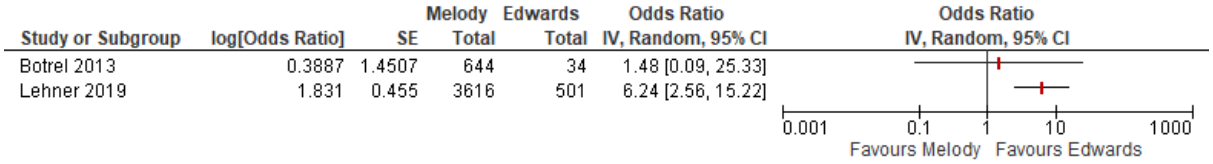

Figure footnote: Outcome: infective endocarditis (refer to Table 9)

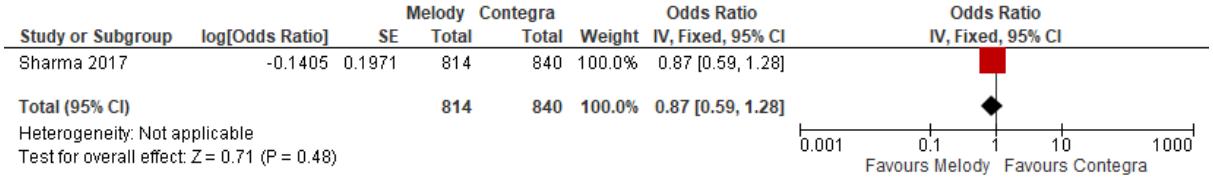

Figure footnote: Outcome: infective endocarditis (refer to Table 9)

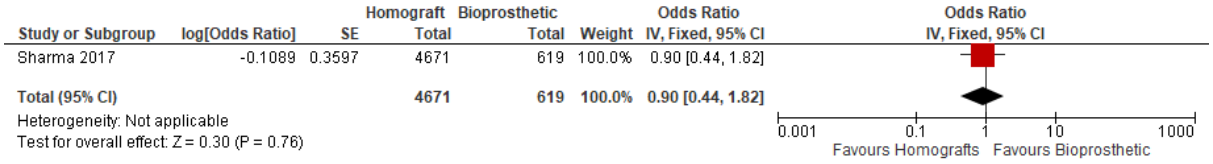

Figure footnote: Outcome: infective endocarditis (refer to Table 9)

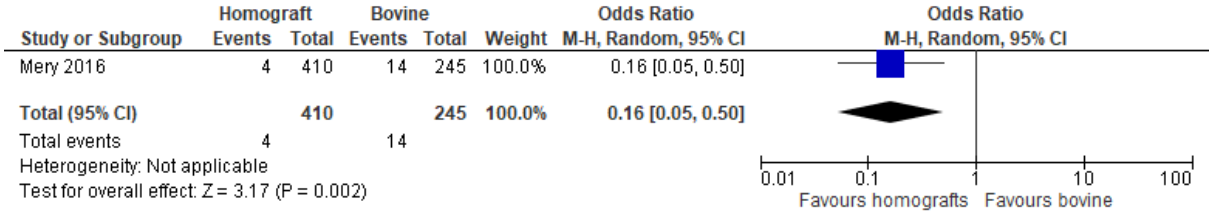

Figure footnote: Outcome: infective endocarditis (refer to Table 9)

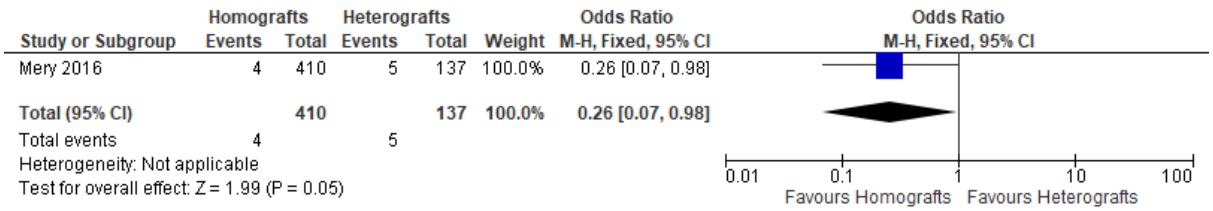

Figure footnote: Outcome: infective endocarditis (refer to Table 9)

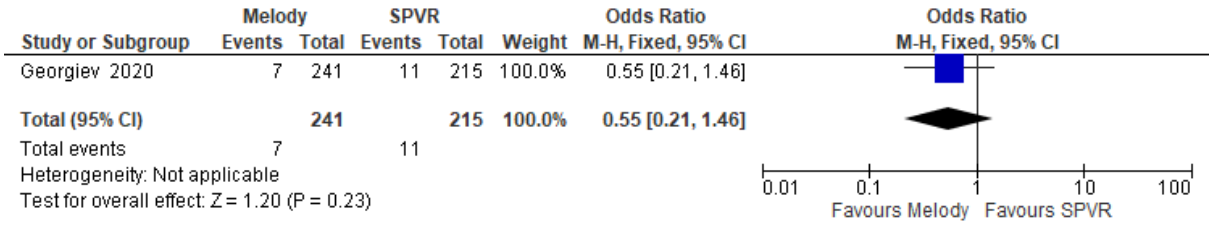

Figure footnote: Outcome: mortality (refer to Table 4)

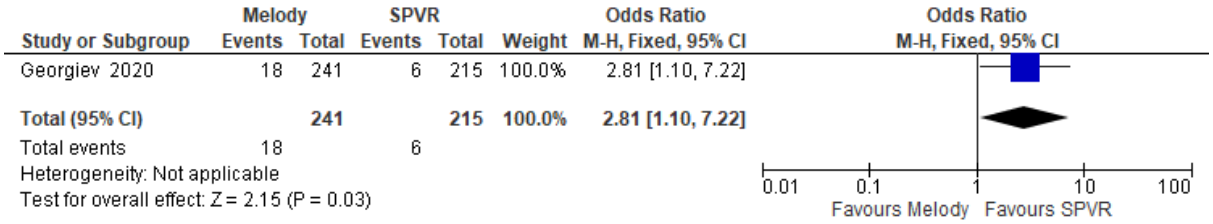

Figure footnote: Outcome: infective endocarditis (refer to Table 9)

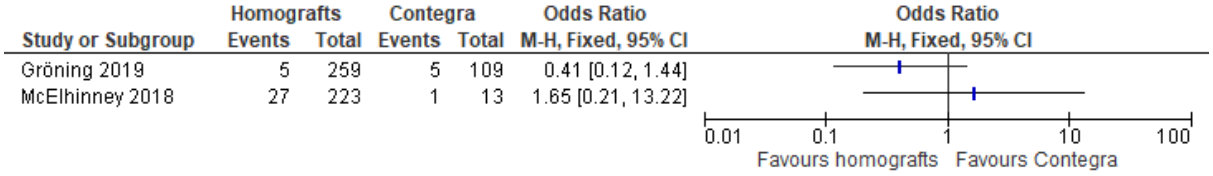

Figure footnote: Outcome: infective endocarditis (refer to Table 9)

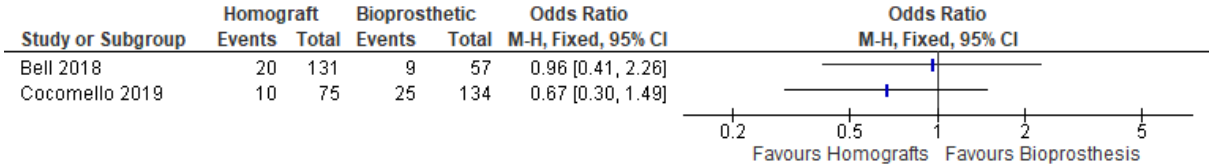

Figure footnote: Outcome: structural valve degeneration (refer to Table 10)

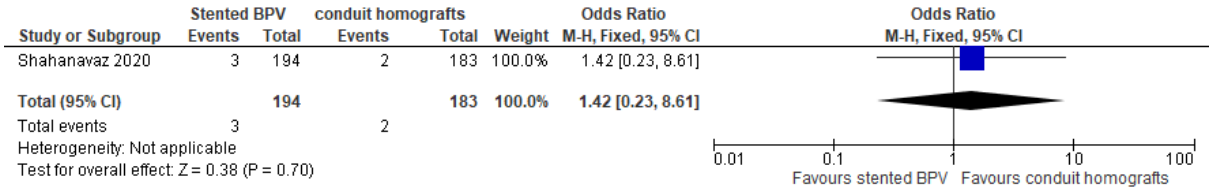

Figure footnote: Outcome: moderate or severe pulmonary regurgitation (refer to Table 6)

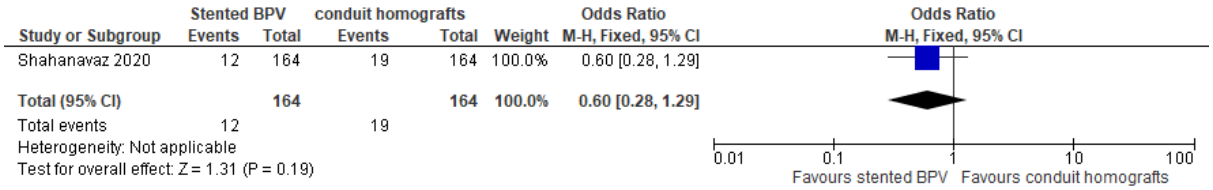

Figure footnote: Outcome: Any serious procedural adverse events (refer to Table 10)