Journal of the American Heart Association

ORIGINAL RESEARCH

Nationwide Registry-Based Analysis of Infective Endocarditis Risk After Pulmonary Valve Replacement

Clara Stammnitz; Dörte Huscher, PhD; Ulrike M. M. Bauer, MD; Aleksandra Urban; Johannes Nordmeyer, MD, PhD; Stephan Schubert, MD; Joachim Photiadis, MD; Felix Berger, MD; Sabine Klaassen, MD; on behalf of the German Competence Network for Congenital Heart Defects Investigators*

BACKGROUND: Infective endocarditis (IE) after pulmonary valve replacements in congenital heart disease is a significant concern. This study aimed to identify specific long-term risk factors for IE after percutaneous pulmonary valve implantation or surgical pulmonary valve replacement.

METHODS AND RESULTS: All patients with congenital heart disease from the National Register for Congenital Heart Defects with at least 1 pulmonary valve replacement before January 2018 were included. A total of 1170 patients (56.3% men, median age at study inclusion 12 [interquartile range {Q1–Q3} 5–20 years]) received 1598 pulmonary valve replacements. IE occurred in 4.8% of patients during a follow-up of total 9397 patient-years (median 10 [Q1–Q3, 6–10] years per patient). After homograft implantation 7 of 558 (1.3%) patients developed IE, after heterograft implantation 31 of 723 (4.3%) patients, and after Melody valve implantation 18 of 241 (7.5%) patients. Edwards Sapien and mechanical valves were used less frequently and remained without IE. The incidence of IE in heterografts excluding Contegra valves was 7 of 278 (2.5%), whereas the incidence of IE in Contegra valves was 24 of 445 (5.4%). The risk of IE was not increased compared with homografts if Contegra valves were excluded from the heterografts (hazard ratio [HR], 2.60; P=0.075). The risk of IE was increased for bovine jugular vein valves, Contegra valves (HR, 6.72; P<0.001), and Melody valves (HR, 5.49; P<0.001), but did not differ between Melody valves and Contegra valves (HR, 1.01; P=0.978).

CONCLUSIONS: Bovine jugular vein valves have the highest risk of IE, irrespective of the mode of deployment, either surgical or percutaneous.

Key Words: adults ■ congenital heart disease ■ endocarditis ■ intervention ■ pediatrics ■ pulmonary valve ■ surgery

Percutaneous pulmonary valve implantation (PPVI) has become a routine practice and alternative to open-heart surgery in congenital heart disease (CHD).[1–3] Right ventricular outflow tract dysfunction frequently occurs in these patients because of the limited lifespan of the material. Surgical pulmonary valve replacement (SPVR) or PPVI for the reconstruction of the right ventricular outflow tract with prosthetic valves increase the risk of infective endocarditis (IE). Several studies with smaller sized cohorts of a few hundred patients have evaluated the short and medium time risks of IE in both modalities.[3–7] The incidence of IE in PPVI has emerged as an increasing concern for follow-up of these patients.[1,8–10] Currently, 2 balloon-expandable

Correspondence to: Sabine Klaassen, MD, Experimental and Clinical Research Center (ECRC), a cooperation between the Max-Delbrück-Center for Molecular Medicine in the Helmholtz Association and the Charité - Universitätsmedizin Berlin, Lindenberger Weg 80, 13125 Berlin, Germany.
E-mail: klaassen@mdc-berlin.de

*A complete list of the German Competence Network for Congenital Heart Defects Investigators can be found in the Supplemental Material.

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.121.022231

For Sources of Funding and Disclosures, see page 9.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- To our knowledge, this nationwide, registry-based study is the largest retrospective analysis comparing the risk of infectious endocarditis (IE) after percutaneous pulmonary valve implantation or surgical pulmonary valve replacement in congenital heart disease.
- Bovine jugular vein valves had the highest risk of IE, irrespective of the mode of deployment, either surgical or percutaneous.
- In the multivariable analysis, the risk of IE was increased in the male sex, in patients with a higher number of previous pulmonary valve replacement and for bovine jugular vein valves (with a similar risk for Melody versus Contegra valves).

What Are the Clinical Implications?

- In anticipating or avoiding the risk of IE in pulmonary valve replacement, the specific type of surgical pulmonary valve replacement and percutaneous pulmonary valve implantation should be considered.
- Surgical homograft replacement is associated with the lowest risk of IE and the surgical use of heterografts excluding Contegra valves does not increase the risk of IE significantly.
- The Melody valve has a high risk of IE that is inherent to bovine jugular vein valves and the interventional procedure per se does not impose a significant risk factor.

Nonstandard Abbreviations and Acronyms

BJV	bovine jugular vein
IE	infective endocarditis
PPVI	percutaneous pulmonary valve implantation
PVR	pulmonary valve replacement
RV-to-PA	right ventricle to pulmonary artery
SPVR	surgical pulmonary valve replacement

devices are available for PPVI: the Melody and the Edwards Sapien valve.[3,5,11] Despite its advantages as a less invasive procedure for right ventricular outflow tract dysfunction, recent studies suggest that IE is more common in Melody valves, compared with homografts.[4–6] Moreover, IE was noticed more frequently in patients with Contegra valves, compared with homografts.[4–6] As both, the Melody valve and the Contegra conduit use bovine jugular vein (BJV) tissue, the use of BJV in general might be critical to the incidence of IE.[12,13] In a systematic search of published research comparing BJV valves with other valve types a higher incidence of IE was found for BJV valves.[14] Registries or databases with comparable large cohorts are limited.[3] In particular, how risk factors differ between patients of different sexes and ages has not yet been sufficiently examined and studies have produced conflicting results.[4–6]

The aim of this nationwide registry-based study was to investigate the long-term incidence of IE in pulmonary valve replacement (PVR) in a large-sized cohort. We sought to identify which clinical baseline characteristics, modes of replacement, number of replacements, and valve types increased the risk of IE. Specifically, we addressed the question of how sex and age affect this pathology.

METHODS

Study Design and Patient Selection

The German NR-CHD (National Register for Congenital Heart Defects) provides a nationwide database with a uniquely large population of patients with CHD. The German NR-CHD represents a community-based population, not primarily recruiting from tertiary centers.[15] The main cardiac diagnosis, all concurrent cardiac anomalies as well as all performed cardiac interventions and operations are recorded in a database using the International Pediatric and Congenital Cardiac Code (IPCCC) published by the International Society for Nomenclature of Paediatric and Congenital Heart Disease (ISNPCHD; http://www.ipccc.net). In addition, extracardiac diagnoses and acquired diseases are recorded using the *International Classification of Diseases, Tenth Revision* (*ICD-10)* code (International Statistical Classification of Diseases and Related Health Problems) published by the World Health Organization (WHO; http://www.who.int/classifications/icd/en/). At the time of screening 51 119 patients were included in the register. Approval by the appropriate Ethics Committee was obtained (Ethikkommission Berlin, Charité, E/KN 14-01-1999). All patients and parents/guardians of patients aged <18 years gave written informed consent.

All patients with CHD with at least 1 SPVR or PPVI before January 1, 2018 were considered for the study. Cases of pulmonary valve–related IE were recorded from January 1, 2007 to December 31, 2017. Patient selection is depicted in Figure S1.

Follow-Up

All patients were followed-up after PVR by data submitted to the NR-CHD. In cases of patients with PVR implantation before January 1, 2007, the time from

implantation to this start date of the observation period was not included in the follow-up. The combined end point was reached when grafts were infected or explanted, or the patient was deceased.

Outcome Definitions

All data and supporting materials are available within the article and the supplementary material.

Every report of a definite or possible IE of patients with PVR was reviewed for the diagnosis and conduit type. The diagnosis of IE was made according to the gold standard, the modified Duke criteria, in the participating centers.[16,17] Only cases with evidence of IE related to the right ventricle–pulmonary artery (RV-to-PA) conduit were evaluated, and only the first incidence of IE was considered. One patient had 2 IEs during the study period. Data were conceived starting from the time of PVR.

Statistical Analysis

Continuous variables are presented with median and interquartile range (Q1–Q3). For categorical variables, counts and percentages are shown. Between-group (different PVR types) differences in sex, IE incidences, number of previous PVR (divided into the groups 0 and ≥1), and pathogens (divided into Staphylococci and other pathogens) were assessed using the Pearson χ^2 test. When >20% of the expected counts were <5, we used Fisher exact test instead. The comparison of the PVR size, age (at implantation, at first PVR, at study inclusion, at IE), the follow-up time, time between PVR and IE, between IE and next PVR, and between first PVR and IE was performed using the Kruskal–Wallis test. IE frequencies were calculated separately for each type of PVR as standardized incidence rates. The impact of the PVR and other patient characteristics on the occurrence of IE was evaluated using a Cox-regression model with time-dependent covariates. As many patients had several different PVR over time, this model helped to determine the influence of the different PVR incorporating all available information of changing PVR of every patient. The selection of variables for the multivariable Cox-regression was based on medical relevance: type of PVR (time-dependent), sex, age at study inclusion (continuous variable), and number of previous PVR. For Cox-regression, PVR types without a single event could not be considered as factors in the analysis. As sensitivity analysis, we then divided the patients into groups according to sex and age at study inclusion and repeated the Cox-regression analyses for these subgroups.

All Cox-regression models were performed with right censoring. Simple Kaplan–Meier curves were generated to depict the IE free survival by PVR up to 11 years of observation including multiple PVR of each patient, which were weighted accordingly. The impact of the IE on the survival of the patients was evaluated using a Cox-regression model with time-dependent covariates adjusted for the other potential impact factors PVR type, sex, number of previous PVR, and age at study inclusion.

P values of ≤0.05 were considered statistically significant; no adjustment for multiple testing was done. Cox-regression and Kaplan–Meier analyses were performed using the "survival" and "survminer" package in R version 3.6.1 (2019-07-05), R Foundation for Statistical Computing, Vienna, Austria (https://www.R-project.org/). All other statistical analyses were performed using IBM SPSS Statistics version 25.0. Armonk, NY (IBM Corp).

RESULTS

Characteristics of Study Population With PVR

A total of 1598 PVR, comprising SPVR and PPVI, were implanted in 1170 patients before January 1, 2018 (Figure S1, Table 1). Melody valves and Edwards Sapien valves were used for PPVI. The SPVR group included aortic and pulmonary homografts, heterografts (Contegra conduits and other heterografts such as bioprosthetic valved conduits with pericardial bovine or porcine material), or mechanical valves (Table S1). Overall, 1096 patients underwent 1305 SPVR and 279 patients underwent 293 PPVI. The most frequent underlying CHD was Tetralogy of Fallot (376 patients, 32.1%), followed by common arterial trunk (156 patients, 13.3%), and congenital aortic valvar stenosis undergoing the Ross procedure (95 patients, 8.1%) (Table S2); 659 patients were males (56.3%) (Table 1). Median (Q1–Q3) age at study inclusion was 12 (5–20) years; 67.7% of patients were aged <18 years, and 32.3% were ≥18 years. By the end of the study 47.1% of the patients had received 1 PVR, 33.5% received 2, 14.5% received 3, 3.9% received 4, 0.8% received 5, and 0.2% received 6 PVR; 18 patients (1.5%) were deceased. Total follow-up was 9397 years (per patient median 10 years). Follow-up for Contegra valves was 2311 years (median 5 years), for heterografts excluding Contegra valves 1423 (median 5 years), for homografts 3613 years (median 7 years), for Melody valves 1001 years (median 4 years), for Edwards Sapien valves 179 years (median 3.5 years), and for mechanical valves 206 years (median 10 years) (Table 1). For 1116 of 1170 patients and 1375 of 1598 PVR the data collection was complete for a 2-year follow-up.

Clinical Characteristics of Patients With IE

Overall, pulmonary valve–related IE occurred in 56 of 1170 patients (4.8%) after a median follow-up of 10 years (Tables 1 and 2). Twelve patients had early

Table 1. Study Population

		PPVI			SPVR					
	Patients	Total	Melody	Edwards Sapien	Total	Heterograft excluding Contegra	Contegra	Homograft	Mechanical valve	*P* value*
No. of PVR, n (%)	1598 (100)	293 (18.3)	241 (15.1)	52 (3.3)	1305 (81.7)	278 (17.4)	445 (27.8)	558 (34.9)	24 (1.5)	
No. of patients, n (%)†	1170 (100)	279 (23.9)	230 (19.7)	52 (4.4)	1096 (93.7)	251 (21.5)	403 (34.4)	523 (44.7)	24 (2.1)	
Male sex, n (% of patients)	659 (56.3)	169 (60.6)	138 (60.0)	33 (63.5)	622 (56.8)	140 (55.8)	242 (60.0)	297 (56.8)	8 (33.3)	0.088
Age at implantation of PVR, y‡	11 (4–17)	17 (13–26)	16 (13–24)	19 (13–29)	9 (3–16)	12 (5–19)	4 (0–9)	12 (5–18)	17 (9–22)	<0.001
PVR size, mm‡,§	20 (17–23)	22 (20–22)	21.5 (20–22)	23 (23–26)	20 (16–23)	22 (18–25)	16 (14–20)	22 (20–24)	23 (21–25)	<0.001
IE, n (%)	56 (4.8‖)	18 (6.1)¶	18 (7.5)¶	0	38 (2.9)¶	7 (2.5)¶	24 (5.4)¶	7 (1.3)¶	0	<0.001
Previous PVR‡	0 (0–1)	1 (1–2)	1 (1–2)	1 (1–2)	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)	<0.001
Age at first PVR, y‡	5 (0–14)	4 (0–12)	4 (0–11)	10 (0–18)	5 (0–14)	6 (0–17)	1 (0–6)	6 (1–15)	11.5 (4–19)	<0.001
Age at study inclusion, y‡	12 (5–20)	13 (8–20)	13 (8–20)	13.5 (8.5–24)	12 (5–20)	12 (5–19)	5 (1–10)	16 (9–22)	22.5 (17–32)	<0.001
<18 y at study inclusion, n (%)	792 (67.7)	191 (68.5)	160 (69.6)	32 (61.5)	749 (68.3)	174 (69.3)	372 (92.3)	294 (56.2)	7 (29.2)	
≥18 y at study inclusion, n (%)	378 (32.3)	88 (31.5)	70 (30.4)	20 (38.5)	347 (31.7)	77 (30.7)	31 (7.7)	229 (43.8)	17 (70.8)	
Follow-up, y‡	10 (6–10)‖	4 (2–6)¶	4 (2–6)¶	3.5 (2–5)¶	6 (3–10)¶	5 (2–8)¶	5 (2–8)¶	7 (4–10)¶	10 (8–10)¶	<0.001
Patient-years of follow-up	9397‖	1180¶	1001¶	179¶	7553¶	1423¶	2311¶	3613¶	206¶	

IE indicates infective endocarditis; PPVI, percutaneous pulmonary valve implantation; PVR, pulmonary valve replacement; and SPVR, surgical pulmonary valve replacement.
*Melody, Edwards Sapien, heterografts excluding Contegra, Contegra, homografts, and mechanical valves were compared.
†Some patients had different pulmonary valve replacement over the observation period.
‡Median (interquartile range).
§The pulmonary valve replacement size was known in 1247 (78.0%) of 1598 pulmonary valve replacement.
‖Calculated based on the number of patients.
¶Calculated based on the number of pulmonary valve replacement.

IE (within 12 months after PVR), and 44 patients had late IE (12 months after PVR); the median time interval (Q1–Q3) was 4 (1–6) years. After homograft implantation, 7 patients (1.3%) developed IE; after heterograft implantation 31 patients (4.3%), and after Melody valve implantation 18 patients (7.5%). The incidence of IE in heterografts excluding Contegra valves was 7 of 278 (2.5%). The incidence of IE in Contegra valves was 24 of 445 (5.4%). Edwards Sapien and mechanical valves were used less frequently and without IE throughout the study population. The Edwards Sapien valve was used in 3.3% of PVR and in a median follow-up time of 3.5 (2–5) years no case of IE occurred. The follow-up time for the Edwards Sapien valves was only somewhat shorter than for the Melody valve, 4 (2–6) years. Nevertheless, Melody valves constituting 15.1% of PVR, had a higher incidence of IE of 7.5%.

The median (Q1–Q3) age at time of implantation of the IE affected PVR was 13.5 (9–20) years, and the median (Q1–Q3) age at time of IE was 16.5 (13–24) years. Of those aged <18 years at study inclusion and those aged ≥18 years, 5.3% and 3.7% developed IE, respectively. The most common pathogen was staphylococcus (32.1%), followed by streptococcus (26.8%) (Table 2, Table S3). In 14 cases (25%), no information about the pathogens was available. In 1 case, no pathogen could be detected (Table 2, Table S3). By the end of the study, 2 (3.6%) of the 56 patients were deceased, both had a Melody valve implanted. One of these patients died because of severe complications

Table 2. Characteristics of Patients With IE After PVR

			SPVR				
	Patients	Melody	Total	Heterograft excluding Contegra	Contegra	Homograft	*P* value*
Patients with IE/patients with PVR, n (%)	56/1170 (4.8)	18/230 (7.8)	38/1096 (3.5)	7/251 (2.8)	24/403 (6.0)	7/523 (1.3)	
PVR with IE/ number of PVR, n (%)	56/1598 (3.5)	18/241 (7.5)	38/1305 (2.9)	7/278 (2.5)	24/445 (5.4)	7/558 (1.3)	
Male sex, n (% of patients)	39 (69.6)	11 (61.1)	28 (73.7)	6 (85.7)	16 (66.7)	6 (85.7)	0.579
PVR size, mm†,‡	20 (18–22)	19 (18–22)	20 (17–22)	25 (20–26)	20 (16–20)	21.5 (16.5–23)	0.071
Age at implantation of PVR, y†	13.5 (9–20)	16 (14–24)	11 (5–18)	18 (9–22)	9 (4–12)	18 (12–21)	0.002
Age at IE, y†	16.5 (13–24)	21.5 (16–29)	15 (11–21)	23 (13–27)	13 (9–18)	19 (12–32)	0.004
Time between PVR and IE, y†	4 (1–6)	5 (2–6)	3 (1–7)	5 (2–11)	3 (1–6)	0 (0–5.5)	0.231
Time between IE and next PVR, mo†	2 (0–8)	0 (0–2)	3 (0–12)	2 (0–25)	3 (0–12)	6 (1–26)	0.193
Previous PVR†	1 (0–2)	1 (1–2)	0 (0–1)	1 (0–2)	0 (0–1)	0 (0–2)	0.006
Age at first PVR, y†	3.5 (0–12)	2.5 (0–9.5)	6 (0–12)	9 (1–16)	4 (0–10)	12 (0–21)	0.437
Time between first PVR and IE, y†	11 (3–16)	18 (13.5–21)	7.5 (2–13)	13 (7–15)	4 (2–11)	5.5 (0–15)	<0.001
Age at study inclusion, y†	12 (7–18)	14.5 (10–21.5)	10.5 (4.5–16)	16 (9–17)	9 (3–13)	12 (7–30)	0.039
<18 y at study inclusion, n (%)	42 (75.0)	11 (61.1)	31 (81.6)	6 (85.7)	21 (87.5)	4 (57.1)	
≥18 y at study inclusion, n (%)	14 (25.0)	7 (38.9)	7 (18.4)	1 (14.3)	3 (12.5)	3 (42.9)	
Pathogen§							0.014‖
Staphylococci, n (%)	18 (32.1)	11 (61.1)	7 (18.4)	1 (14.3)	4 (16.7)	2 (28.6)	
Streptococci, n (%)	15 (26.8)	5 (27.8)	10 (26.3)	3 (42.9)	7 (29.2)	0	
Other pathogens, n (%)	8 (14.3)	1 (5.6)	7 (18.4)	2 (28.6)	4 (16.7)	1 (14.3)	

IE indicates infective endocarditis; PVR, pulmonary valve replacement; and SPVR, surgical pulmonary valve replacement.
*Melody valves, heterografts excluding Contegra, Contegra valves, and homografts, were compared.
†Median (interquartile range).
‡The pulmonary valve replacement size was known in 35 (62.5%) of 56 pulmonary valve replacements.
§Negative blood culture in one case (heterograft), and not available in 14 (25.0%) cases (4 homografts, 1 heterograft excluding Contegra, 8 Contegra valves, 1 Melody valve).
‖Staphylococci were compared with other pathogens.

subsequent to IE of the Melody valve. The infection was caused by staphylococcus aureus, the patient was female, and aged 18 years at time of IE. In the other patient, also female, a Melody valve was implanted in 2008, and subsequently a Contegra valve in 2010. She had IE of the Contegra valve in 2012, and died in 2015 with the Contegra valve still implanted from a cause unrelated to IE.

Time to IE, Incidence Rates, and IE Free Survival

The median time interval between PVR and IE was 0 years for homografts, 5 years for heterografts excluding Contegra valves, 3 years for Contegra valves, and 5 years for Melody valves (Table 2). Fouty-four patients (78.6%) underwent PVR after the IE, and 16 patients (28.6%) received PVR in the first 30 days after the IE. By the end of the study, patients with IE had received more PVR (median 3) compared with patients without IE (median 2).

Annualized incidence rates for homografts, heterografts excluding Contegra valves, Contegra valves, and Melody valves were 0.2% (0.2 cases per 100 patient-year), 0.5%, 1.0%, and 1.8%, respectively. IE free survival for homografts, heterografts excluding Contegra valves, Contegra valves, and Melody valves was 99.3%, 99.6%, 97.9%, 98.3% after 1 year, 98.6%, 98.3%, 94.8%, 93.1% after 5 years, and 98.6%, 91.5%, 91.4%, 84.5% after 10 years (Figure—Panel A; log rank $P<0.001$), respectively. IE showed no significant influence on the overall survival of the patients (hazard ratio [HR], 3.57; $P=0.200$).

Risk Factors for the Occurrence of IE

In order to identify risk factors for IE, we performed univariable Cox-regression analysis. The risk of IE was higher for Contegra valves (HR, 5.62; 95% CI, 2.42–13.07; $P<0.001$) and Melody valves (HR, 7.81; 95% CI, 3.20–19.05; $P<0.001$) compared with homografts (Table S4). The risk of IE was not increased for heterografts excluding Contegra valves (HR, 2.60; 95% CI, 0.91–7.43; $P=0.074$). The PVR size was known in 1247 of 1598 PVR (Table 1). The size of the PVR and the age at study inclusion had no significant influence on the risk of IE. Age at study inclusion ranged between 0 and 81 years, median 12 (Q1–Q3, 5–20). The risk of IE was increased in males compared with females (HR, 1.95; 95% CI, 1.10–3.44; $P=0.022$; Table S4).

The multivariable Cox-regression was performed with the covariables PVR, sex, number of previous PVR, and age at study inclusion. The multivariable analysis confirmed the significant influence of male sex (HR, 1.81; 95% CI, 1.02–3.20; $P=0.044$; Figure—Panel B) and a higher number of previous PVR (HR, 1.45; 95% CI, 1.04–2.00; $P=0.026$; Figure—Panel C) on the risk of IE (Table 3). The age at the time of study inclusion had no significant influence in the multivariable Cox-regression. The risk of IE for patients with heterografts excluding Contegra valves was not significantly higher than for homografts (HR, 2.60; 95% CI, 0.91–7.43; $P=0.075$), whereas the risk of patients with Contegra valves (HR, 6.72; 95% CI, 2.80–16.16; $P<0.001$) and Melody valves (HR, 5.49; 95% CI, 2.12–14.19; $P<0.001$) was increased (Figure—Panel D). The group of patients with a Melody valve had more often previous PVR compared with the group of patients with a Contegra valve (Table 1, $P<0.001$). The risk of IE for Melody valves did not differ significantly from that of Contegra valves (HR, 1.01; $P=0.978$; Table 3). The risk of IE for PPVI compared with SPVR was not different (HR, 1.84; $P=0.077$), but if the Contegra valves were excluded, the risk of IE for PPVI was significantly higher compared with SPVR (HR, 3.07; 95% CI, 1.34–7.06; $P=0.008$). Patients were divided into groups according to sex (females and males) and age at study inclusion (<18 and ≥18 years), respectively (Tables S4 through S6). In females and in patients aged ≥18 years bovine jugular valves (Contegra and Melody valves) were especially associated with an increased risk of IE. A higher number of previous PVR increased the risk of IE only for males and patients aged <18 years. Because of the low number of events in females and patients ≥18 years these sex- and age-specific results may not be overinterpreted.

DISCUSSION

To our knowledge, this study is the largest retrospective analysis comparing the risk of IE after SPVR and PPVI. Moreover, this nationwide, registry-based study investigates the potential differences between males and females, and children and adults on the impact of covariates and types of PVR on the occurrence of IE.

BJV valves have the highest risk of IE, irrespective of the mode of deployment, either surgical or percutaneous. Overall, there was no difference in the risk of IE in PPVI compared with SPVR. The highest risk of IE in patients with SPVR was found for Contegra valves and in patients with PPVI for Melody valves. Excluding the Contegra valve in the multivariable analysis lead to an increased risk of PPVI compared with SPVR. Patients with homografts had the lowest incidence of IE. There were no cases of IE in patients with Edwards Sapien and mechanical valves. Other significant risk factors for IE were male sex and higher numbers of previous PVR. PVR size showed no significant influence on the risk of IE despite the wide age range across pediatric and adult patient subcohorts.

Percutaneous Versus Surgical PVR

Some single-center studies with a maximal number of 677 patients[4] in 1 study investigated and compared the

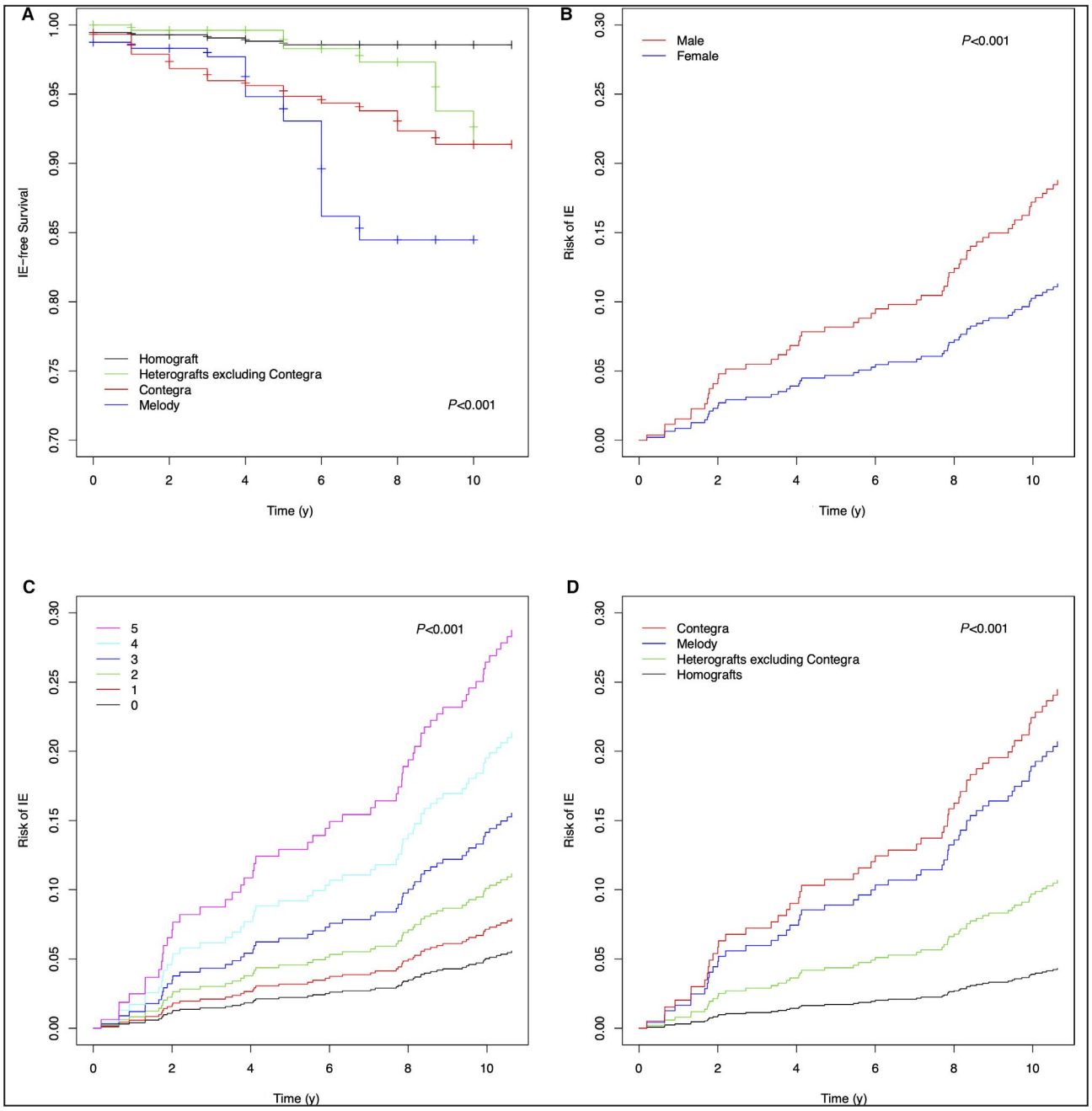


Figure 1. Survival free from infective endocarditis (IE).
A, Kaplan−Meier analysis of IE free survival for homograft, heterograft excluding Contegra, Contegra, and Melody valves (from top to bottom); *P* value from log-rank test. **B** through **D**, Results from the multivariable cox-regression model with time-dependent covariates; *P* values from likelihood ratio test. **B**, The risk of IE was higher for males than for females. **C**, The risk of IE increased with the number of previous pulmonary valve replacements. **D**, The risk of IE was higher for Contegra, Melody, and heterografts excluding Contegra valves compared with homografts.

occurrence of IE in PPVI and SPVR.[3–7] Our nationwide study had the longest follow-up time with median of 10 years and the largest number of patients with a total follow-up of 9397 years. The study had a wide age range at study inclusion, but recruited predominantly children, adolescents, and young adults reflecting the underlying CHD.

We focused on the most commonly used PVR groups, such as homografts, heterografts, and Melody valves. Homografts had the lowest incidence of pulmonary valve−related IE, followed by heterografts. Melody valves had the highest incidence of pulmonary valve−related IE. In the multivariable analysis the risk of patients with Melody and Contegra valves was increased

Table 3. Impact Factors on the Occurrence of IE in Multivariable Cox-Regression

	HR (95% CI)	*P* value
All types of PVR		
Type of PVR		
Homograft	1	
Heterograft excl. Contegra	2.60 (0.91–7.43)	0.075
Contegra	6.72 (2.80–16.16)	<0.001
Melody	5.49 (2.12–14.19)	<0.001
Sex		
Female	1	
Male	1.81 (1.02–3.20)	0.044
No. of previous PVR	1.45 (1.04–2.00)	0.026
Age at study inclusion, y	1.02 (0.99–1.04)	0.141
Subgroup with Contegra or Melody		
Type of PVR		
Contegra	1	
Melody	1.01 (0.44–2.32)	0.978
Sex		
Female	1	
Male	1.34 (0.71–2.52)	0.365
No. of previous PVR	1.36 (0.92–2.02)	0.127
Age at study inclusion, y	1.02 (0.99–1.05)	0.200

HR indicates hazard ratio; IE, infective endocarditis; and PVR, pulmonary valve replacement.

compared with patients with homografts and heterografts excluding Contegra. The group of patients with a Melody valve had more often previous PVR compared with the group of patients with a Contegra valve, which probably led to the increased risk of IE for Melody valves in the univariable Cox-regression.

The incidence rates of IE for the Melody valve, the Contegra valve, and for homografts in our study was in the same range of what has been reported in systematic reviews.[14,18] In studies using Cox regression models an increased risk of IE for patients with Melody and Contegra valves compared with patients with homografts was found.[4–6] Whether the risk of IE for the Melody valve or for the Contegra valve was higher differed in these studies, maybe to the small number of patients included. In our large study, in the multivariable analysis, the risk of IE for the Melody valve was not different from the Contegra valve.

In this study heterografts were more frequently used for SPVR than homografts, while in other studies homograft implantation was more frequent than heterograft implantation.[3,4,6] In 1 previous German study more heterografts, specifically Contegra valves, than homografts were used for SPVR.[5] In most studies Contegra valves were the primary choice for a heterograft.[4–6] The high number of Contegra valves in this study has provided the advantage to specifically look at this valve type with a good set of patient characteristics. In the multivariable analysis Contegra valves showed the highest risk of IE although it was not statistically different from the risk of Melody valves. Excluding the Contegra valve in the multivariable analysis lead to an increased risk of PPVI compared with SPVR. Therefore, when comparing PPVI and SPVR, the ratio of specific types of SPVR needs to be considered. We show that because of the large number of Contegra valves in our study we see no increased risk of PPVI versus SPVR. This further specifies the Contegra valve, a bovine jugular valve, as a risk factor for IE.

Increased Risk of IE in Patients With BJV Valves

A higher incidence of IE with BJV valves than in other types of RV-to-PA conduits has been demonstrated.[7,12,13] Studies specifically reported on an increased incidence of IE in patients with Melody[1,8–10] and Contegra[19,20] valves. The incidence of IE between catheter-based bovine valves and surgically implanted bovine valves was not different, suggesting that the method of implantation was not relevant for possible future infection.[14] Higher thrombogenicity, lower rate of endothelialization, and tropism for microorganisms to the BJV material of Melody and Contegra valves was suggested.[7] Differences in bacterial adhesion to BJV versus bovine pericardial leaflets was debated.[21,22]

PPVI and the Risk of IE

When the 2 valve types Melody and Edwards Sapien were compared, the implantation of the Edwards Sapien valve, made from bovine pericardial tissue leaflets, seemed more suitable to reduce the risk of post PPVI IE.[5,11,23–25] One potential factor for the increased risk of IE for the Melody valve was the residual RV-to-PA pressure gradient at the time of PPVI.[1,2] We found no cases of pulmonary valve–related IE among the patients with Edwards Sapien valves. A low risk of IE for Edwards Sapien has been reported.[26,27] In our study and in others, Edwards Sapien valves had only a slightly shorter follow-up time, but were still implanted less frequently than the Melody valves. The Melody valves constituting 15.1% of PVR in this study, had a remarkable incidence of IE of 7.5%. So despite the assumption that the PPVI procedure carries an increased risk of IE,[28] we rather assume that the procedure is safe and that the material of the PVR might be crucial. The Edwards Sapien valve seems useful for PPVI in high risk subgroups for IE, but larger numbers and longer follow-up are needed.

A high number of previous PVR could be a risk factor for IE. The first PVR, usually a surgical valve, is implanted at an early age, then followed by PPVR at

a later time point. In this study age at first PVR was not significant for IE in Cox-regression and this variable could be excluded in our study. Another explanation which is much more likely is that patients with a higher number of PVR might have produced microscopic lesions during procedural steps or turbulences leading to non-bacterial thrombotic endocarditis that can turn infective after any transient bacteremia.[29] In an in vitro study of explanted Melody valves pathologic examination revealed the presence of granulocytes in the preexisting surgical conduit in all cases, denoting that the space between the Melody valve stent and the underlying conduit with little neovascularization might lead to a compartment that cannot be reached by antibiotics.[30] This might also partly explain the higher incidence of Melody valves for IE in this study, caused by progressive deterioration of the underlying conduit used as a Melody landing zone.

Study Limitations

The retrospective nature of the study may be regarded as a limitation. No exact data on the hemodynamics of the RV-to-PA conduit before IE were available. Differences here, such as potentially higher flow velocities across the Melody valve or Contegra conduit compared with homografts, may be a contributor to different IE rates and may be as important as differences in valve structure or tissue characteristics. Therefore we can only speculate on the pathogenesis of IE, specifically on the incidence of late IE in our study which might be related to the hemodynamic situation. The size of PVR was only available in 78.0% of cases. PVR size showed no significant influence on the risk of IE as already reported in previous studies.[5,6] The CIs were partially wide, which is probably difficult to avoid in a rare condition such as IE related to the RV-to-PA conduit. Despite our large study population, the number of IE events in the subgroup analysis for females and patients aged ≥18 years was low for covariable adjustment. Therefore, the results of the multivariable sex- and age-specific subgroup analysis could be biased and should be considered as a preliminary indication of differences which require further investigation.

CONCLUSIONS

Homograft replacement is the method of choice to avoid the risk of IE. Further basic research is needed to determine why BJV valves have the highest risk of IE, irrespective of the mode of deployment, either surgical or percutaneous. The risk of IE is not significantly higher for heterografts than for homografts if Contegra valves are excluded. Other significant risk factors for IE are male sex and higher numbers of previous PVR. The Edwards Sapien valve seems useful for PPVI in high risk subgroups for IE, but larger numbers and longer follow-up are needed.

ARTICLE INFORMATION

Received April 26, 2021; accepted December 23, 2021.

Affiliations

Department of Pediatric Cardiology, Charité - Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany (C.S., F.B., S.K.); Competence Network for Congenital Heart Defects, National Register for Congenital Heart Defects, Berlin, Germany (C.S., U.M.M.B., A.U.); Institute of Biometry and Clinical Epidemiology, Charité - Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany (D.H.); DZHK (German Centre for Cardiovascular Research), Berlin, Germany (U.M.M.B.); Department of Congenital Heart Disease - Pediatric Cardiology, German Heart Center Berlin, Berlin, Germany (J.N., S.S., F.B.); Center for Congenital Heart Disease/Pediatric Cardiology, Heart- and Diabetescenter NRW, University Clinic of Ruhr-University Bochum, Bad Oeynhausen, Germany (S.S.); Department of Congenital Heart Surgery - Pediatric Heart Surgery, German Heart Center Berlin, Berlin, Germany (J.P.); DZHK (German Centre for Cardiovascular Research), partner site Berlin, Berlin, Germany (F.B., S.K.); and Experimental and Clinical Research Center (ECRC), a cooperation between the Max-Delbrück-Center for Molecular Medicine in the Helmholtz Association and the Charité - Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany (S.K.).

Sources of Funding

This work was supported by the Competence Network for Congenital Heart Defects (Federal Ministry of Education and Research/grant number 01GI0601) and the National Register for Congenital Heart Defects (Federal Ministry of Education and Research/grant number 01KX2140).

Disclosures

Huscher received travel compensation from Actelion, Boehringer-Ingelheim, and Shire. Schubert is Proctor and Consultant for Abbott, Edwards Lifescience, and Medtronic and received honoraries and travel compensation. The remaining authors have no disclosures to report.

Supplemental Material

Appendix S1
Tables S1–S6
Figure S1

REFERENCES

1. McElhinney DB, Benson LN, Eicken A, Kreutzer J, Padera RF, Zahn EM. Infective endocarditis after transcatheter pulmonary valve replacement using the Melody valve: combined results of 3 prospective North American and European studies. *Circ Cardiovasc Interv*. 2013;6:292–300. doi: 10.1161/CIRCINTERVENTIONS.112.000087
2. Nordmeyer J, Ewert P, Gewillig M, AlJufan M, Carminati M, Kretschmar O, Uebing A, Dähnert I, Röhle R, Schneider H, et al. Acute and midterm outcomes of the post-approval MELODY Registry: a multicentre registry of transcatheter pulmonary valve implantation. *Eur Heart J*. 2019;40:2255–2264. doi: 10.1093/eurheartj/ehz201
3. Georgiev S, Ewert P, Eicken A, Hager A, Horer J, Cleuziou J, Meierhofer C, Tanase D. Munich comparative study: prospective long-term outcome of the transcatheter melody valve versus surgical pulmonary bioprosthesis with up to 12 years of follow-up. *Circ Cardiovasc Interv*. 2020;13:e008963. doi: 10.1161/CIRCINTERVENTIONS.119.008963
4. Van Dijck I, Budts W, Cools B, Eyskens B, Boshoff DE, Heying R, Frerich S, Vanagt WY, Troost E, Gewillig M. Infective endocarditis of a transcatheter pulmonary valve in comparison with surgical implants. *Heart*. 2015;101:788–793. doi: 10.1136/heartjnl-2014-306761
5. Haas NA, Bach S, Vcasna R, Laser KT, Sandica E, Blanz U, Jakob A, Dietl M, Fischer M, Kanaan M, et al. The risk of bacterial endocarditis after percutaneous and surgical biological pulmonary

valve implantation. *Int J Cardiol*. 2018;268:55–60. doi: 10.1016/j.ijcard.2018.04.138
6. Groning M, Tahri NB, Sondergaard L, Helvind M, Ersboll MK, Orbaek AH. Infective endocarditis in right ventricular outflow tract conduits: a register-based comparison of homografts, Contegra grafts and Melody transcatheter valves. *Eur J Cardiothorac Surg*. 2019;56:87–93. doi: 10.1093/ejcts/ezy478
7. Malekzadeh-Milani S, Ladouceur M, Iserin L, Bonnet D, Boudjemline Y. Incidence and outcomes of right-sided endocarditis in patients with congenital heart disease after surgical or transcatheter pulmonary valve implantation. *J Thorac Cardiovasc Surg*. 2014;148:2253–2259. doi: 10.1016/j.jtcvs.2014.07.097
8. Buber J, Bergersen L, Lock JE, Gauvreau K, Esch JJ, Landzberg MJ, Valente AM, Sandora TJ, Marshall AC. Bloodstream infections occurring in patients with percutaneously implanted bioprosthetic pulmonary valve: a single-center experience. *Circ Cardiovasc Interv*. 2013;6:301–310. doi: 10.1161/CIRCINTERVENTIONS.112.000348
9. McElhinney DB, Sondergaard L, Armstrong AK, Bergersen L, Padera RF, Balzer DT, Lung T-H, Berger F, Zahn EM, Gray RG, et al. Endocarditis after transcatheter pulmonary valve replacement. *J Am Coll Cardiol*. 2018;72:2717–2728. doi: 10.1016/j.jacc.2018.09.039
10. Malekzadeh-Milani S, Ladouceur M, Patel M, Boughenou FM, Iserin L, Bonnet D, Boudjemline Y. Incidence and predictors of Melody(R) valve endocarditis: a prospective study. *Arch Cardiovasc Dis*. 2015;108:97–106.
11. Hascoet S, Mauri L, Claude C, Fournier E, Lourtet J, Riou JY, Brenot P, Petit J. Infective endocarditis risk after percutaneous pulmonary valve implantation with the Melody and Sapien valves. *JACC Cardiovasc Interv*. 2017;10:510–517.
12. Mery CM, Guzman-Pruneda FA, De Leon LE, Zhang W, Terwelp MD, Bocchini CE, Adachi I, Heinle JS, McKenzie ED, Fraser CD Jr. Risk factors for development of endocarditis and reintervention in patients undergoing right ventricle to pulmonary artery valved conduit placement. *J Thorac Cardiovasc Surg*. 2016;151:432–439, 441.e1–2.
13. Ugaki S, Rutledge J, Al Aklabi M, Ross DB, Adatia I, Rebeyka IM. An increased incidence of conduit endocarditis in patients receiving bovine jugular vein grafts compared to cryopreserved homograft for right ventricular outflow reconstruction. *Ann Thorac Surg*. 2015;99:140–146.
14. Sharma A, Cote AT, Hosking MCK, Harris KC. A systematic review of infective endocarditis in patients with bovine jugular vein valves compared with other valve types. *JACC Cardiovasc Interv*. 2017;10:1449–1458.
15. Helm PC, Koerten MA, Abdul-Khaliq H, Baumgartner H, Kececioglu D, Bauer UM. Representativeness of the German National Register for Congenital Heart Defects: a clinically oriented analysis. *Cardiol Young*. 2016;26:921–926. doi: 10.1017/S1047951115001547
16. Habib G, Hoen B, Tornos P, Thuny F, Prendergast B, Vilacosta I, Moreillon P, de Jesus Antunes M, Thilen U, Lekakis J, et al. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the International Society of Chemotherapy (ISC) for Infection and Cancer. *Eur Heart J*. 2009;30:2369-2413.
17. Li JS, Sexton DJ, Mick N, Nettles R, Fowler VG Jr, Ryan T, Bashore T, Corey GR. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis*. 2000;30:633–638. doi: 10.1086/313753
18. Abdelghani M, Nassif M, Blom NA, Van Mourik MS, Straver B, Koolbergen DR, Kluin J, Tijssen JG, Mulder BJM, Bouma BJ, et al. Infective endocarditis after Melody valve implantation in the pulmonary position: a systematic review. *J Am Heart Assoc*. 2018;7:e008163. doi: 10.1161/JAHA.117.008163
19. Boethig D, Westhoff-Bleck M, Hecker H, Ono M, Goerler A, Sarikouch S, Breymann T. Bovine jugular veins in the pulmonary position in adults—5 years' experience with 64 implantations. *Thorac Cardiovasc Surg*. 2009;57:196–201. doi: 10.1055/s-0029-1185394
20. Albanesi F, Sekarski N, Lambrou D, Von Segesser LK, Berdajs DA. Incidence and risk factors for Contegra graft infection following right ventricular outflow tract reconstruction: long-term results. *Eur J Cardiothorac Surg*. 2014;45:1070–1074. doi: 10.1093/ejcts/ezt579
21. Jalal Z, Galmiche L, Lebeaux D, Villemain O, Brugada G, Patel M, Ghigo JM, Beloin C, Boudjemline Y. Selective propensity of bovine jugular vein material to bacterial adhesions: an in-vitro study. *Int J Cardiol*. 2015;198:201–205. doi: 10.1016/j.ijcard.2015.07.004
22. Veloso TR, Claes J, Van Kerckhoven S, Ditkowski B, Hurtado-Aguilar LG, Jockenhoevel S, Mela P, Jashari R, Gewillig M, Hoylaerts MF, et al. Bacterial adherence to graft tissues in static and flow conditions. *J Thorac Cardiovasc Surg*. 2018;155:325–332.e4. doi: 10.1016/j.jtcvs.2017.06.014
23. Lehner A, Haas NA, Dietl M, Jakob A, Schulze-Neick I, Dalla Pozza R, Rodriguez SF, Fischer M. The risk of infective endocarditis following interventional pulmonary valve implantation: a meta-analysis. *J Cardiol*. 2019;74:197–205. doi: 10.1016/j.jjcc.2019.04.007
24. Biernacka EK, Ruzyllo W, Demkow M, Kowalski M, Spiewak M, Piotrowski W, Kusmierczyk M, Banas S, Rozanski J, Hoffman P. Transcatheter pulmonary valve implantation in patients with right ventricular outflow tract dysfunction: early and mid-term results. *J Invasive Cardiol*. 2015;27:E82–E89.
25. Tanase D, Ewert P, Hager A, Georgiev S, Cleuziou J, Hess J, Eicken A. Infective endocarditis after percutaneous pulmonary valve implantation—a long-term single centre experience. *Int J Cardiol*. 2018;265:47–51. doi: 10.1016/j.ijcard.2018.04.094
26. Hascoet S, Dalla Pozza R, Bentham J, Carere RG, Kanaan M, Ewert P, Biernacka EK, Kretschmar O, Deutsch C, Lecerf F, et al. Early outcomes of percutaneous pulmonary valve implantation using the Edwards SAPIEN 3 transcatheter heart valve system. *EuroIntervention*. 2019;14:1378–1385. doi: 10.4244/EIJ-D-18-01035
27. Kenny D, Rhodes JF, Fleming GA, Kar S, Zahn EM, Vincent J, Shirali GS, Gorelick J, Fogel MA, Fahey JT, et al. 3-year outcomes of the Edwards SAPIEN transcatheter heart valve for conduit failure in the pulmonary position from the COMPASSION Multicenter Clinical Trial. *JACC Cardiovasc Interv*. 2018;11:1920–1929.
28. Jalal Z, Galmiche L, Beloin C, Boudjemline Y. Impact of percutaneous pulmonary valve implantation procedural steps on leaflets histology and mechanical behaviour: an in vitro study. *Arch Cardiovasc Dis*. 2016;109:465–475. doi: 10.1016/j.acvd.2016.01.015
29. Uebing A, Rigby ML. The problem of infective endocarditis after transcatheter pulmonary valve implantation. *Heart*. 2015;101:749–751. doi: 10.1136/heartjnl-2014-307287
30. Schneider H, Vogt M, Boekenkamp R, Hoerer J, Eicken A, Foth R, Kriebel T, Paul T, Sigler M. Melody transcatheter valve: histopathology and clinical implications of nine explanted devices. *Int J Cardiol*. 2015;189:124–131. doi: 10.1016/j.ijcard.2015.04.067

Supplemental Material

CONSORTIUM Collaborators

German Competence Network for Congenital Heart Defects Investigators:
Gunter Kerst, Jaime F. Vazquez-Jimenez, Dimitrios Gkalpakiotis, Andrea Schedifka, Gernot Buheitel, Joachim Streble, Kai Thorsten Laser, Eugen Sandica, Burkhard Trusen, Felix Berger, Oliver Miera, Stanislav Ovroutski, Björn Peters, Katharina Schmitt, Stephan Schubert. Joachim Photiadis, Bernd Opgen-Rhein, Katja Weiss, Christoph Berns, Carl-Christian Blumenthal-Barby, Thomas Boeckel, Guido Haverkämper, Andreas Kästner, Heike Koch, Christian Köpcke, Frank Streichan, Jens Timme, Birgit Franzbach, Gabriela Senft, Frank Beyer, Klaus Winter, Johannes Breuer, Bahman Esmailzadeh, Martin Schneider, Boulos Asfour, Jens Bahlmann, Eberhard Griese, Trong Phi Lê, Joachim Hebe, Jan-Hendrik Nürnberg, Annette Magsaam, Ronald Müller, Ludger Potthoff, Renate Voigt, Tim Krüger, Hubert Gerleve, Ulrich Kleideiter, Dirk Schneider-Kulla, Jürgen Krülls-Münch, Elmo Feil, Thomas Menke, Martin Lehn, Antje Heilmann, Helge Tomczak, Otto N. Krogmann, Gleb Tarusinov, Michael Scheid, Ertan Mayatepek, Frank Pillekamp, Artur Lichtenberg, Christiane Terpeluk, Bruno Kolterer, Sven Dittrich, Ulrike Gundlach, Robert Cesnjevar, Ulrich Neudorf, Geert Morf, Anoosh Esmaeili, Stephan Backhoff, Brigitte Stiller, Friedhelm Beyersdorf, Johannes Kroll, Nicole Häffner, Jannos Siaplaouras, Antje Masri-Zada, Christian Jux, Andreas Böning, Hakan Akintürk, Thomas Paul, Matthias Sigler, Theodor Tirilomis, Gabriele Schürer, Johannes Hartmann, Ralph Grabitz, Uta Liebaug, Claudius Rotzsch, Rainer Kozlik-Feldmann, Jörg Sachweh, Arlindo Riso, Stefan Renz, Andreas Schemm, Bernd Friedrich, Otmar Schlobohm, Philipp Beerbaum, Dietmar Böthig, Alexander Horke, Johann Bauersachs, Mechthild Westhoff-Bleck, Matthias Gorenflo, Matthias Karck, Tsvetomir Loukanov, Hermann Schrüfer, Martin Wilken, Hashim Abdul-Khaliq, Tanja Rädle-Hurst, Axel Rentzsch, Hans-Joachim Schäfers, Hagen Reichert, Thomas Kriebel, Arnulf Boysen, Anselm Uebing, Joachim Thomas Cremer, Jens Scheewe, Regina Buchholz-Berdau, Peter Möller, Wolfgang Ram, Konrad Brockmeier, Gerardus B. W. E. Bennink, Alex Gillor, Tim Niehues, Peter Terhoeven, Steffen Leidig, Ingo Dähnert, Peter Kinzel, Martin Kostelka, Liane Kändler, Martin Bethge, Stefan Köster, Christoph Schröder, Jens Karstedt, Uwe Seitz, Christoph Kampmann, Christian-Friedrich Vahl, Frank Stahl, Mojtaba Abedini, Joachim Müller-Scholden, Peter Ewert, Alfred Hager, Harald Kaemmerer, Nicole Nagdyman, Jörg Schoetzau, Oktay Tutarel, Rüdiger Lange, Jürgen Hörer, Nikolaus A. Haas, Lale Rosenthal, Michael Hauser, Alexander Roithmaier, Hans-Gerd Kehl, Edward Malec, Helmut Baumgartner, Gerhard Diller, Roswitha Bahle, Gerald Hofner, Stefan Zink, Roland Reif, Helmut Singer, Christoph Parlasca, Matthias W. Freund, Michael Schumacher, Oliver Dewald, Christine Darrelmann, Reinald Motz, Olaf Willmann, Norbert Schmiedl, Peter Quick, Dirk Hillebrand, Stephan Michele Eiselt, Torsten Nekarda, Michael Eberhard, Georg Baier, Frank Uhlemann, Ioannis Tzanavaros, Alexander Beyer, Gudrun Binz, Steffen Hess, Thomas Teufel, Ronald-Peter Handke, Michael Hofbeck, Renate Kaulitz, Ludger Sieverding, Christian Schlensak, Christian Apitz, Michael Kaestner, Christoph Kupferschmid, Jürgen Holtvogt, Carl-Friedrich Wippermann, Andreas Heusch, Johannes Wirbelauer, Wolfgang Brosi.

Table S1. Type of specific PVR of study population

Type of specific PVR, N (%)	N=1598	PVR with IE, N (%)
Contegra® conduit	445 (27.9)	24 (5.4)
Aortic homograft	363 (22.7)	5 (1.4)
Melody™ transcatheter pulmonary valve	241 (15.1)	18 (7.5)
Pulmonary homograft	190 (11.9)	2 (1.1)
Hancock® Bioprosthetic Valved Conduit	157 (9.8)	5 (3.2)
Edwards SAPIEN© valve	52 (3.3)	0
Carpentier-Edwards© valved conduit	30 (1.9)	0
Matrix Patch™	24 (1.5)	1 (4.2)
Labcor® Valved Pulmonar Conduit	22 (1.4)	0
St. Jude Medical	18 (1.1)	0
Shelhigh Pulmonic Valve Conduit	14 (0.9)	0
MatrixPplus	13 (0.8)	1 (7.7)
Capentier-Edwards PERIMOUNT ©	12 (0.8)	0
Carbomedics®	6 (0.4)	0
Dacron® valved conduit	6 (0.4)	0
MHH TE homograft	5 (0.3)	0

IE, infective endocarditis; PVR, pulmonary valve replacement

Table S2. Underlying congenital heart disease diagnoses of study population

Principal Diagnosis according to EPCC	EPCC code	Category of CHD	No. of Patients, N (%)	Male sex, N (%)	Age at first PVR, yrs*	Age at study inclusion, yrs*
			1170	659 (56.3)	5 (0-14)	12 (5-20)
Tetralogy of Fallot	01.01.01	1†	376 (32.1)	190 (50.5)	13 (5-21)	17 (10-27)
Common arterial trunk (truncus arteriosus)	09.01.01	2‡	156 (13.3)	74 (47.4)	0 (0-0)	7 (2-14)
Aortic valvar stenosis: congenital	09.15.01	3§	95 (8.1)	73 (76.8)	9 (3-15)	12 (5-19)
Pulmonary atresia + ventricular septal defect (VSD) + systemic-to-pulmonary collateral artery(ies) (MAPCA(s)),	01.01.25	1†	93 (8.0)	54 (58.1)	2 (1-7)	7 (3-14.5)
Pulmonary atresia + ventricular septal defect (VSD) (including Fallot type)	01.01.06	1†	82 (7.0)	46 (56.1)	1 (0-4)	9 (5-17)
Pulmonary valvar stenosis: congenital	09.05.04	3§	49 (4.2)	34 (69.4)	17 (10-27)	19 (12.5-29.5)
Discordant ventriculo-arterial connections (TGA)	01.05.01	2‡	47 (4.0)	29 (61.7)	3 (0-10)	8 (1-17)
Double outlet right ventricle: Fallot Type (subaortic or doubly committed ventricular septal defect & pulmonary stenosis)	01.01.17	2‡	47 (4.0)	29 (61.7)	1 (0-10)	5 (1-13)
Double outlet right ventricle: transposition type (subpulmonary ventricular septal defect)	01.01.18	2‡	45 (3.9)	31 (68.9)	2 (0-6.5)	8 (1-13)
Pulmonary atresia + intact ventricular septum	01.01.07	3§	29 (2.5)	18 (62.1)	8 (3.5-12.5)	12 (8-17)
Absent pulmonary valve syndrome: Fallot-type	09.05.25	1†	19 (1.6)	7 (36.8)	2 (0-13)	11 (1-15)
Congenitally corrected transposition of great arteries (discordant atrioventricular & ventriculo-arterial connections)	01.01.03	2‡	16 (1.4)	7 (43.8)	6 (2-18)	23 (5-27)
Others			100 (8.6)	58 (58.0)	7.5 (1-16)	13 (4-21)

EPCC. European Paediatric Cardiac Code (IPCCC Short List) - 1 April 2012, with ICD-9, ICD-10, STS/EACTS Short List crossmapping; CHD, congenital heart defect.
* Median (interquartile range)

† Tetralogy of Fallot and variants

‡ Atrioventricular and-or ventriculo-arterial connections abnormal

§ Abnormalities of ventriculo-arterial valves and great arteries

Table S3. Specific pathogens in IE of PVR

				SPVR		
	Patients	Melody (18)	Total (38)	Heterograft (hancock and others) (7)	Contegra (24)	Homograft (7)
Staphylococcus	18 (32.1)	11 (61.1)	7 (18.4)	1 (14.3)	4 (16.7)	2 (28.6)
Staphylococcus aureus	11 (19.6)	8 (44.4)	3 (7.9)	0	3 (12.5)	0
Staphylococcus epidermidis	3 (5.4)	1 (5.6)	2 (5.3)	1 (14.3)	0	1 (14.3)
Staphylococcus hominis	1 (1.8)	0	1 (2.6)	0	0	1 (14.3)
Staphylococcus lugdunensis	1 (1.8)	1 (5.6)	0	0	0	0
Staphylococcus sanguinus	1 (1.8)	0	1 (2.6)	0	1 (4.2)	0
Other coagulase-negative staphylococci	1 (1.8)	1 (5.6)	0	0	0	0
Streptococcus	15 (26.8)	5 (27.8)	10 (26.3)	3 (42.9)	7 (25.9)	0
Streptococcus gordonii	1 (1.8)	0	1 (2.6)	0	1 (4.2)	0
Streptococcus anginosus	2 (3.6)	1 (5.6)	1 (2.6)	0	1 (4.2)	0
Streptococcus intermedius	1 (1.8)	1 (5.6)	0	0	0	0
Streptococcus mitis	2 (3.6)	0	2 (5.3)	2 (28.6)	0	0
Streptococcus oralis	1 (1.8)	0	1 (2.6)	0	1 (4.2)	0
Streptococcus oralis / mitis	1 (1.8)	1 (5.6)	0	0	0	0
Streptococcus parasanguinis	2 (3.6)	1 (5.6)	1 (2.6)	0	1 (4.2)	0
Streptococcus sanguinis	3 (5.4)	0	3 (7.9)	1 (14.3)	2 (8.3)	0
Streptococcus viridans	1 (1.8)	1 (5.6)	0	0	0	0
Other streptococci	1 (1.8)	0	1 (2.6)	0	1 (4.2)	0
Abiotrophia defectiva	1 (1.8)	0	1 (2.6)	0	1 (4.2)	0
Brevibacterium spp.	1 (1.8)	0	1 (2.6)	0	1 (4.2)	0

Cardiobacterium hominis	1 (1.8)	0	1 (2.6)	1 (14.3)	0	0
Coxiella burnetti	1 (1.8)	0	1 (2.6)	0	1 (4.2)	0
Enterococcus faecium	1 (1.8)	0	1 (2.6)	0	0	1 (14.3)
Oligella ureolytica	1 (1.8)	0	1 (2.6)	1 (14.3)	0	0
Rothia mucilanginosa	1 (1.8)	1 (5.6)	0	0	0	0
Candida	1 (1.8)	0	1 (2.6)	0	1 (4.2)	0
Negative blood culture	1 (1.8)	0	1 (2.6)	0	1 (4.2)	0
Not available	14 (25)	1 (5.6)	13 (34.2)	1 (14.3)	8 (33.3)	4 (57.1)

IE, infective endocarditis; PVR, pulmonary valve replacement

Table S4. Impact factors on the occurrence of IE in univariable Cox-regression

	All patients		Female sex		Male sex		Patients <18 years at study inclusion		Patients ≥18 years at study inclusion	
Subgroup	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Type of PVR										
Homograft	1		1		1		1		1	
Heterograft Excl. Contegra	2.60 (0.91-7.43)	0.074	2.44 (0.15-39.06)	0.528	2.76 (0.89-8.58)	0.079	3.14 (0.89-11.15)	0.076	1.19 (0.12-11.41)	0.883
Contegra	5.62 (2.42-13.07)	<0.001	13.55 (1.69-108.48)	0.014	4.25 (1.65-10.91)	0.003	5.12 (1.75-14.97)	0.003	8.06 (1.63-39.98)	0.011
Melody	7.81 (3.20-19.05)	<0.001	22.90 (2.78-188.30)	0.004	5.01 (1.79-14.01)	0.002	6.05 (1.89-19.40)	0.002	12.05 (3.00-48.32)	<0.001
PVR size (mm) *	0.97 (0.89-1.04)	0.371	0.95 (0.82-1.11)	0.545	0.96 (0.88-1.06)	0.417	1.02 (0.93-1.12)	0.610	0.85 (0.65-1.11)	0.233
Sex										
Female	1		-		-		1		1	
Male	1.95 (1.10-3.44)	0.022	-		-		2.03 (1.02-4.04)	0.044	1.57 (0.54-4.51)	0.407
Number of previous PVR	1.63 (1.23-2.17)	<0.001	1.41 (0.82-2.40)	0.214	1.71 (1.22-2.39)	0.002	1.71 (1.21-2.42)	0.002	1.39 (0.79-2.45)	0.255
Age at study inclusion, yrs	0.99 (0.97-1.02)	0.569	1.01 (0.97-1.05)	0.586	0.99 (0.96-1.02)	0.450	-		-	-
<18	1		1		1		-		-	-
≥18	0.63 (0.86-2.89)	0.139	0.81 (0.46-3.35)	0.674	0.62 (0.75-3.53)	0.222	-		-	-

IE, infective endocarditis; PVR, pulmonary valve replacement; n.a., not applicable; HR, hazard ratio; CI, confidence interval.*PVR size was known in 1247/1598 PVR

Table S5. Sex and age-specific impact factors on the occurrence of IE in multivariable Cox-regression

	Female sex*		Male sex		Patients <18 years at study inclusion		Patients ≥18 years at study inclusion*	
All types of PVR	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Type of PVR								
Homograft	1		1		1		1	
Heterograft excluding Contegra	2.18 (0.14-35.12)	0.584	2.51 (0.80-7.87)	0.116	2.92 (0.82-10.37)	0.098	1.23 (0.13-11.89)	0.858
Contegra	24.39 (2.84-209.54)	0.004	4.55 (1.71-12.15)	0.003	5.54 (1.89-16.23)	0.002	8.13 (1.64-40.33)	0.010
Melody	24.30 (2.71-217.64)	0.004	3.22 (1.08-9.62)	0.036	3.60 (1.08-12.05)	0.038	16.30 (3.37-78.80)	<0.001
Sex								
Female	-		-		1		1	
Male	-		-		1.90 (0.95-3.80)	0.069	1.67 (0.57-4.85)	0.350
Number of previous PVR	1.10 (0.58-2.07)	0.773	1.61 (1.11-2.36)	0.013	1.70 (1.16-2.48)	0.006	0.76 (0.34-1.73)	0.517
Age at study inclusion, yrs	1.05 (1.01-1.09)	0.025	1.00 (0.98-1.04)	0.662	-			
Subgroup with Contegra or Melody								
Type of PVR								
Contegra	1		1		1		1	
Melody	1.09 (0.29-4.13)	0.904	0.97 (0.33-2.83)	0.952	0.90 (0.35-2.31)	0.822	2.01 (0.39-10.35)	0.404
Sex								
Female	-		-		1		1	
Male	-		-		1.23 (0.59-2.56)	0.586	1.98 (0.55-7.10)	0.297
Number of previous PVR	1.20 (0.64-2.27)	0.565	1.49 (0.90-2.48)	0.126	1.54 (0.97-2.45)	0.068	0.98 (0.43-2.22)	0.952
Age at study inclusion, yrs	1.04 (0.98-1.09)	0.178	1.01 (0.98-1.05)	0.524	-		-	

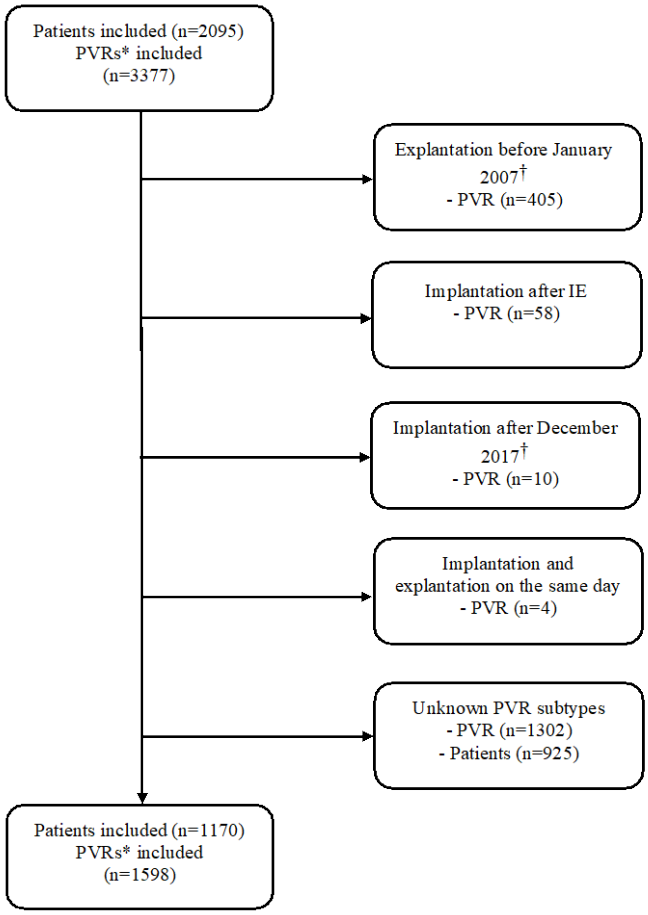
IE, infective endocarditis; PVR, pulmonary valve replacement; HR, hazard ratio; CI, confidence interval.
*For female sex (17 IE) and for patients ≥ 18 years (14 IE) the model was with four covariables potentially overspecified.

Table S6. Characteristics of patients with IE after PVR according to sex and age at study inclusion

		Sex		Age at study inclusion, y	
	Total	Males	Females	<18	≥18
Patients with IE, N					
Total	56	39	17	42	14
Melody	18	11	7	11	7
SPVR	38	28	10	31	7
Heterograft excluding Contegra	7	6	1	6	1
Contegra	24	16	8	21	3
Homograft	7	6	1	4	3
Number of previous PVR*					
Total	0 (0-2)	1 (0-2)	1 (0-1)	1 (0-2)	0.5 (0-1)
Melody	1 (1-2)	1 (1-2)	1 (1-3)	2 (1-2)	1 (1-2)
Heterograft excluding Contegra	0 (0-1)	1 (0-2)	0 (0-0)	1 (0-2)	0 (0-0)
Contegra	0 (0-1)	0.5 (0-1)	0 (0-1)	0 (0-1)	0 (0-0)
Homograft	0 (0-2)	0 (0-2.5)	0 (0-0)	1 (0-3.5)	0 (0-0)
Patient-Years of Follow-Up					
Total†	274	188	86	209	65
PPVI‡					
Melody‡	73	37	36	47	26
SPVR‡	134	89	45	110	24
Heterograft‡ excluding Contegra	46	37	9	37	9
Contegra	75	44	31	72	3
Homograft‡	13	8	5	1	12

*Median (interquartile range), †calculated based on the number of patients, ‡ calculated based on the number of PVR.

Figure S1. Study flow chart.



Study design for the recruitment of patients with PVR in the National Register for Congenital Heart Defects, Berlin, Germany. *Number of PVR in the patients. †Cases of pulmonary-valve-related IE were recorded during the period of January 1st, 2007 until December 31st, 2017.
PVR, pulmonary valve replacement; IE, infective endocarditis; CHD, congenital heart defect.