

## Infective endocarditis after transcatheter approach versus surgical pulmonary valve replacement: A meta-analysis

*Cerrahi pulmoner kapak replasmanına karşı transkateter yaklaşım sonrası enfektif endokardit: Meta-analiz*

Elif Ijlal Çekirdekçi<sup>1</sup>, Barış Bugan<sup>2</sup>, Lütfi Çağatay Onar<sup>3</sup>, Ahmet Çekirdekçi<sup>4</sup>

*Institution where the research was done:*  
University of Kyrenia, Kyrenia, Turkish Republic of Northern Cyprus

*Author Affiliations:*

<sup>1</sup>Department of Cardiology, University of Kyrenia, Kyrenia, Turkish Republic of Northern Cyprus

<sup>2</sup>Department of Cardiology, Gülhane Training and Research Hospital, Ankara, Türkiye

<sup>3</sup>Department of Cardiovascular Surgery, Dr. Ismail Fehmi Cumalioglu Government Hospital, Tekirdağ, Türkiye

<sup>4</sup>Department of Cardiovascular Surgery, Kütahya Health Science University, Kütahya, Türkiye

### ABSTRACT

**Background:** In this meta-analysis, we aimed to assess the risk of infective endocarditis in transcatheter versus surgical pulmonary valve replacement patients.

**Methods:** We systematically searched PubMed, Cochrane, EMBASE, Scopus, and Web of Science for the studies that reported the event rate of infective endocarditis in both transcatheter and surgical pulmonary valve replacement between December 2012 and December 2021. Random-effects model was used in the meta-analysis.

**Results:** Fifteen comparison groups with 4,706 patients were included. The mean follow-up was 38.5±3.7 months. Patients with transcatheter pulmonary valve replacement had a higher risk of infective endocarditis than patients receiving surgically replaced valves (OR 2.68, 95% CI: 1.83-3.93, p<0.00001). The calculated absolute risk difference was 0.03 (95% CI: 0.01-0.05), indicating that if 1,000 patients received a surgical valve replacement, 30 cases of infective endocarditis would be prevented. A meta-regression of follow-up time on the incidence of infective endocarditis was not statistically significant (p=0.753).

**Conclusion:** Although transcatheter pulmonary valve replacement is a feasible alternative to surgical replacement in severe right ventricular outflow tract dysfunction, the higher incidence of infective endocarditis in transcatheter replacement remains a significant concern. Regarding this analysis, surgical treatment of right ventricular outflow tract dysfunction is still a viable option in patients with prohibitive risk.

**Keywords:** Infective endocarditis, surgical pulmonary valve replacement, transcatheter pulmonary valve implantation.

### ÖZ

**Amaç:** Bu çalışmada transkatetere kıyasla cerrahi pulmoner kapak replasmanı yapılan hastalarda enfektif endokardit riski değerlendirildi.

**Çalışma planı:** Aralık 2012 - Aralık 2021 tarihleri arasında hem transkateter hem de cerrahi pulmoner kapak replasmanında enfektif endokardit oranını bildiren çalışmalar için PubMed, Cochrane, EMBASE, Scopus, and Web of Science sistematik olarak tarandı. Meta-analizde rastgele etkiler modeli kullanıldı.

**Bulgular:** Çalışmaya 4706 hasta ile 15 karşılaştırma grubu dahil edildi. Ortalama takip süresi 38.5±3.7 ay idi. Transkateter pulmoner kapak replasmanı yapılan hastalarda cerrahi kapak replasmanı yapılan hastalara kıyasla enfektif endokardit riski daha yüksekti (OR 2.68, %95 GA: 1.83-3.93, p<0.00001). Hesaplanan mutlak risk farkı 0.03 idi (%95 GA: 0.01-0.05); bu da 1000 hastaya cerrahi kapak replasmanı yapılması durumunda 30 enfektif endokardit olgusunun önleneceğini gösterdi. Enfektif endokardit insidansı üzerine takip süresinin meta-regresyon analizi istatistiksel olarak anlamlı değildi (p=0.753).

**Sonuç:** Şiddetli sağ ventrikül çıkım yolu disfonksiyonunda transkateter pulmoner kapak replasmanı cerrahi replasmana uygulanabilir bir alternatif olmasına rağmen, transkateter replasmanda enfektif endokardit insidansının yüksek olması önemli bir endişe kaynağı olmaya devam etmektedir. Bu analizle ilgili olarak, sağ ventrikül çıkım yolu disfonksiyonunun cerrahi tedavisi, engelleyici riski olan hastalarda hala uygulanabilir bir seçenektir.

**Anahtar sözcükler:** Enfektif endokardit, cerrahi pulmoner kapak replasmanı, transkateter pulmoner kapak replasmanı.

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**Correspondence:** Elif Ijlal Çekirdekçi, MD. Department of Cardiology, University of Kyrenia, 99320 Kyrenia, Turkish Republic of Northern Cyprus.

Tel: +90 542 - 876 88 99 e-mail: elifcekirdekci@hotmail.com

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A dysfunctional or absent pulmonary valve or the right ventricular outflow tract (RVOT) obstruction are essential components in many congenital heart defects. Various types of bioprostheses, cryopreserved pulmonic or aortic homografts, Contegra™ grafts (ContegraVR Pulmonary Valved Conduit, Medtronic Inc., Minneapolis, MN, USA), Melody™ valves (Melody Transcatheter Pulmonary Valve, Medtronic Inc., Minneapolis, MN, USA), and the Sapien™ transcatheter valves (Edwards Lifesciences, Irvine, CA, USA) are used for the RVOT reconstruction in patients with congenital heart disease (CHD).<sup>11</sup> Homografts are used as right ventricle-to-pulmonary artery (RV-PA) conduits, and the Contegra™ grafts are made of bovine jugular veins with a trileaflet venous valve. Both are implanted via sternotomy with the use of extracorporeal circulation. Since limited longevity of bioprosthetic valves and conduits requiring multiple redo-sternotomies, transcatheter (percutaneous) pulmonary valve (TPV) with a Melody™ valve which is made of a bovine jugular vein with a trileaflet valve sutured into an expandable platinum stent implantation, was first described in 2000 by Bonhoeffer et al.<sup>12</sup> to reduce the number of redo-operations.

Additionally, self-expandable TPV Venus P-valve (Venus MedTech Inc., Hangzhou, China) and Harmony (Medtronic Inc., Minneapolis, MN, USA) has been used recently in patients with large RVOT. Since transcatheter pulmonary valves have outstanding features over open heart surgery, such as short recovery time, the lack of need extracorporeal circulation, prolonged stent patency, good leaflet function, rapid life normalization, improved psychosocial outcomes, and the cheapness of the process, they appear to be a very competitive and crucial therapeutic option for pulmonary valve replacement in patients with CHD.<sup>13,41</sup> However, despite their advantages, infective endocarditis (IE) of the transcatheter pulmonary valves emerges as a potential threat for the long-term compared to homograft.

In this meta-analysis, we aimed to compare the incidence of IE in TPV replacement (TPVR) recipients and surgical pulmonary valve replacement (SPVR) patients to identify risk factors for IE and to evaluate the possible impact on mortality.

## **MATERIALS AND METHODS**

### **Search strategy and study selection**

We systematically searched PubMed, Cochrane, EMBASE, Scopus, and Web of Science for the studies that reported the event rate of IE in both TPVR and SPVR and published on or prior to December 22, 2021.

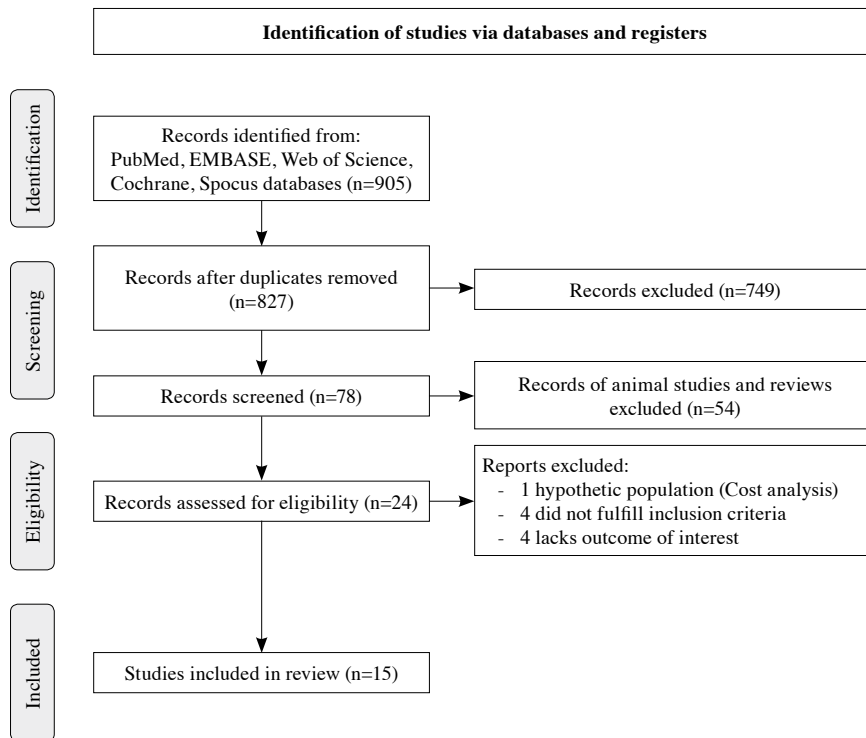
We also performed a manual search from case series studies, reviews, editorials, and commentaries to find relevant studies. The search was limited to English articles.

The EndNote and Rayyan software was used to remove any duplicates and select eligible studies from the database findings and other sources (lists of references in included studies).<sup>15,61</sup> Two authors independently screened titles and abstracts for eligibility of the studies using the following query terms: TPVR/implantation, SPVR/implantation, IE, and prosthetic valve endocarditis. Studies were considered eligible, if they compared TPVR with SPVR and reported IE incidence. Studies were excluded if they were published only in the form of an abstract or a conference presentation, duplicate publications and if the interest of the outcomes was not clearly declared. Any discrepancies were resolved after a discussion with the senior author. The systematic search of the literature was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA) (Figure 1).<sup>171</sup>

Two authors independently assessed the quality of studies according to the Cochrane assessment method was used to analyze study quality. The primary outcome was the incidence rate of IE between TPVR and SPVR. The secondary outcome was overall mortality. In addition, the following study and patient-related information were extracted from the main paper and accompanying supplemental material: publication year, study design, years of inclusion, follow-up time, male sex, age, baseline CHD, type of intervention, primary and secondary endpoints.

### **Statistical analysis**

Statistical analysis was performed using the Review Manager (RevMan) version 5.3 software (Nordic Cochrane Centre, The Cochrane Collaboration, 2012, Copenhagen, Denmark) to calculate the pooled effect size with odds ratio (OR) and 95% confidence intervals (CI) by Mantel-Haenszel method and random effect model. The I<sup>2</sup> statistics evaluated heterogeneity of studies, and we considered ≤25% as low, 26% to 50% as moderate, 51% to 75% as high, and >75% as very high. A meta-regression was performed to analyze the impact of moderator variables on outcomes of interest, particularly the follow-up period on the incidence of IE. A two-sided *p* value of <0.05 was considered statistically significant. Sensitivity analyses were performed for the primary endpoint by removing individual studies on the pooled effect. The Egger and Begg tests and visual inspection of funnel plots evaluated publication bias. The meta-regression



**Figure 1.** PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart for literature search and study selection.

was performed using Comprehensive Meta-analysis software.<sup>[8]</sup>

## RESULTS

A total of 905 published articles were identified from electronic databases and other sources. After screening the title and abstract of possible relevant publications, 78 papers were selected retrieved as complete manuscripts, and 15 articles with 4,706 patients (2,376 males, 2,330 females) were included for comparative analysis (Figure 1). No randomized trials were comparing transcatheter valves to surgical valves among the included studies. The Cochrane assessment method was used to analyze study quality.

The overall study population consisted of 4,706 patients from 15 comparison groups with a mean age of  $21.6 \pm 1.2$  years (95% CI: 19.2-24.0 years). The mean follow-up was  $38.5 \pm 3.7$  months (95% CI: 31.2-45.9). The design and characteristics of the studies included in the analysis are presented in Table 1.<sup>[9-23]</sup> The baseline characteristics of the pooled cohort are presented in Table 2. The TPVR group included higher patients with an underlying diagnosis of transposition of great arteries (TGA), ventricular septal defect (VSD),

pulmonary stenosis (PS) (8% vs. 0.5%,  $p < 0.0001$ ), and truncus arteriosus (9.2 vs. 3.9%,  $p = 0.0006$ ). The surgical group, on the other hand, had higher mean percentages of younger ( $26.1 \pm 13.3$  vs.  $22.7 \pm 13.8$  years,  $p = 0.01$ ) and underweight ( $56 \pm 25$  vs.  $52 \pm 25$  kg,  $p = 0.03$ ) patients.

In all patients, the diagnosis was established according to modified Duke criteria.<sup>[24]</sup> The incidence of IE was significantly higher in patients who received transcatheter pulmonary valves compared to patients receiving surgically replaced pulmonary valves (OR: 2.68, 95% CI: 1.83 to 3.93,  $p < 0.00001$ ). Heterogeneity within the included studies was low ( $I^2 = 5\%$ ) (Figure 2). Forest and Funnel plots of included studies are shown in supplemental Figure 1. Exclusion of the study with maximum weight did not change the analysis results (OR: 2.72, 95% CI: 1.86-3.99,  $p < 0.00001$ ). Among TPVR patients, the most frequently isolated pathogens in blood culture were *Staphylococcus aureus* (16.9%) and HACEK (5.6%), and *Streptococcus viridians* (3.9%). Blood culture was negative in 5.6%; most cases were polymicrobial (Table 3). The calculated absolute risk difference (RD) was 0.03 (95% CI: 0.01-0.05), indicating that if 1,000 patients received a surgical

**Table 1. Design and characteristics of the studies included in the analysis**

Study	Follow-up time (TPVR vs SPVR)	Design	Years of inclusion	Children/adult	Type TPVR	Type of SPVR	Primary endpoints	Secondary endpoints
Alassas et al. <sup>[9]</sup>	56±24 vs. 89±46 months	Non-randomized, retrospective, single-center	1990-2015	Children and adults	Melody, Sapien	New homograft implantation	Reported (no early mortality in either group)	<ul style="list-style-type: none"> <li>Periprocedural complications</li> <li>Mortality during follow-up</li> <li>Endocarditis</li> <li>Redo PVR</li> <li>Significant PR (≥ moderate)</li> <li>Peak systolic gradient</li> <li>Length of hospital stay</li> </ul>
Andresen et al. <sup>[10]</sup>	1 year (both)	Non-randomized, prospective, single-center	June 2011-October 2014	Children and adults	Melody, Sapien	Stented bioprosthesis/valved conduit/Homo-graft	Mortality, reintervention, or reoperation	<ul style="list-style-type: none"> <li>Periprocedural complications</li> <li>Endocarditis</li> <li>Redo PVR</li> <li>Length of hospital stay</li> </ul>
Caughron et al. <sup>[11]</sup>	3 years (both)	Non-randomized, retrospective, single-centre	January 2007-August 2017	Adults	Melody, Sapien	Stented bioprosthesis/valved conduit/Homo-graft	Procedural and clinical outcomes	<ul style="list-style-type: none"> <li>Mortality during follow-up</li> <li>Endocarditis</li> <li>Redo PVR</li> <li>Significant PR (≥ moderate)</li> <li>Peak systolic gradient</li> <li>Length of hospital stay</li> </ul>
Dilber et al. <sup>[12]</sup>	Not specified	Non-randomized, retrospective, single-center	May 2005-November 2010	Children and adults	Melody	Not specified	Reported (implicit in the text-no early mortality in either group)	<ul style="list-style-type: none"> <li>Periprocedural complications</li> <li>Mortality during follow-up</li> <li>Infective endocarditis</li> <li>Redo PVR</li> <li>Significant PR (severe)</li> </ul>
Enezate et al. <sup>[13]</sup>	30-day (both)	Non-randomized, retrospective, multi-centre	The Nation-wide Read-missions Database (NRD)-2014	Children and adults	Mixed	Not specified	<ul style="list-style-type: none"> <li>All-cause in-hospital mortality</li> <li>Median LOS of index hospitali-zation</li> <li>Total charges of index hospitali-zation</li> </ul>	<ul style="list-style-type: none"> <li>Post-procedural bleeding</li> <li>Mechanical complications</li> <li>Vascular complications</li> <li>Infective endocarditis</li> <li>Total charges of index hospitalization and 30-day readmission rates</li> </ul>
Grønning et al. <sup>[15]</sup>	Median 8.3; 3.6-13.1 years (Homograft)/median 6.0; 3.2-8.2 years (Contegra)/median 3.9; 1.0-6.8 years (Melody)	Non-randomized, retrospective, single-center	May 1977-September 2016	Children and adults	Melody	Valved conduit/Homograft	Infective endo-carditis	Mortality
Georgiev et al. <sup>[14]</sup>	5.4 years (3 months to 12.5 years)	Non-randomized, prospective, single-center	January 2006 and December 2018	Children and adults	Melody	Homograft/Hancock/Contegra/other valves	<ul style="list-style-type: none"> <li>Mortality</li> <li>Valve failure of both valves requiring implantation of a new pulmonary valve</li> </ul>	Infective endocarditis
Haas et al. <sup>[16]</sup>	2.4±1.6 (Sapiens)/4.3±1.5 (Melody) vs. 3.1±1.8 (Contegra)/2.5±2.3 (homograft)/0.2±1.4 (Hancock)	Non-randomized, retrospective, single-center	2010-2015	Children	Melody, Sapien	Stented bioprosthesis/Valved conduit/Homograft	Not reported	Endocarditis
Hribernik et al. <sup>[17]</sup>	Median 17; 0-116 months vs. median 47; 0-243 months	Non-randomized, retrospective, single-center	August 1998 to April 2020	Children and adults	Melody, Venus P-valve	Stented bioprosthesis/valved conduit/non-valved conduit	<ul style="list-style-type: none"> <li>Reintervention on the RV-PA segment</li> <li>Mortality</li> <li>Infective endocarditis</li> </ul>	<ul style="list-style-type: none"> <li>Change in NYHA class</li> <li>Change in echocardiographic and magnetic resonance imaging (MRI)-derived volume and pressure measurements</li> </ul>

**Table 1. Continued**

Study	Follow-up time (TPVR vs. SPVR)	Design	Years of inclusion	Children/adult	Type TPVR	Type of SPVR	Primary endpoint	Secondary endpoints
Lluri et al. <sup>[18]</sup>	2.2 (IQR 1.0, 3.1) years vs. 2.8 (IQR 0.9, 4.0)	Non-randomized, retrospective, single-center	October 2010-September 2016	Children and adults	Melody, Sapien	Bioprostheses (not specified) 70 (52%) of SPVR	Endocarditis	<ul style="list-style-type: none"> <li>Length of hospital stay</li> <li>Significant PR (severe)</li> <li>NYHA Class I after 6 months</li> <li>30-day mortality</li> <li>Mortality during follow-up</li> <li>Endocarditis</li> </ul>
Malekzadeh-Milani et al. <sup>[19]</sup>	24.1 (95% CI, 19.9-29.9) months vs. 23.8 (95% CI, 17.5-32.5)	Non-randomized, retrospective, single-center	January 2009-June 2013	Children and adults	Melody	Stented bioprostheses/valved or non-valved conduit/homograft	Not reported	<ul style="list-style-type: none"> <li>Mortality during follow-up</li> <li>Endocarditis</li> </ul>
O'Donnell et al. <sup>[20]</sup>	2.9 (IQR 2.0-4.6) vs. 2.9 (1.7-3.9) years	Non-randomized, retrospective, multi-center	October 2009-May 2015	Children and adults	Melody	Stented or stentless bioprostheses/valved conduit/homograft	Not reported	<ul style="list-style-type: none"> <li>Endocarditis</li> </ul>
Ou-Yang et al. <sup>[21]</sup>	Median 36; 24 to 60 months	Non-randomized, retrospective, multi-center	May 2014-April 2017	Children and adults	Venus P-valve	Homograft	Reported (no early mortality in either group)	<ul style="list-style-type: none"> <li>Periprocedural complications</li> <li>Rehospitalization during follow-up</li> <li>Endocarditis</li> <li>Redo PVR</li> <li>Change in echocardiographic parameters</li> <li>NYHA Class</li> </ul>
Sharma et al. <sup>[22]</sup>	18.7±17 vs. 31.6±22 months	Non-randomized, retrospective, single-center	2010-2015	Children	Melody	Stentless bioprostheses	<ul style="list-style-type: none"> <li>Reintervention for valvar dysfunction complications</li> <li>Mortality during follow-up</li> </ul>	<ul style="list-style-type: none"> <li>Periprocedural complications</li> <li>Mortality during follow-up</li> <li>Endocarditis</li> <li>Redo PVR</li> <li>Significant PR (severe)</li> <li>Peak systolic gradient</li> <li>Length of hospital stay</li> </ul>
Van Dijke et al. <sup>[23]</sup>	2.8 (IQR 2.4) vs. 6.5 (IQR 9.2, homografts)/8.8 (IQR 7.7, Contegra) years	Non-randomized, retrospective, single-center	1989-2013	Children and adults	Melody	Valved conduit/homograft	Not reported	<ul style="list-style-type: none"> <li>Mortality</li> <li>Endocarditis</li> <li>Redo PVR</li> </ul>

TPVR: Percutaneous pulmonary valve replacement; SPVR: Surgical pulmonary valve replacement; PVR: Pulmonary valve replacement; PR: Pulmonary regurgitation; LOS: \_\_\_\_\_; RV: Right ventricle; PA: Pulmonary artery; NYHA: New York Heart Association; MRI: Magnetic resonance imaging; IQR: Interquartile range.

**Table 2. Demographic and clinical characteristics**

	TPVR		SPVR		Median	95% CI	I <sup>2</sup> (%)	p
	Mean±SD	n	Mean±SD	n				
Age (year)	26.1±13.3		22.7±13.8		2.59	0.52-4.66	94	0.01
Weight (kg)	56±25		52±25		5.06	0.37-9.75	87	0.03
Pre-procedural peak gradient (mmHg)	48±25		31±23		10.63	-2.68-23.95	98	0.12
	n	%	n	%	OR	95% CI	I <sup>2</sup> (%)	p
Sex								
Male	647/1,434	45.1	1,729/3,272	52.8	1.02	0.85-1.23	23	0.80
Diagnosis								
Tetralogy of Fallot	404/918	44	1107/2568	43	0.69	0.44-1.06	82	0.09
TGA	17/441	3.9	14/721	2	1.56	0.69-3.54	0	0.20
TGA, VSD, PS	16/200	8	3/545	0.5	12.08	3.96-36.93	0	<0.0001
Truncus arteriosus	86/929	9.2	110/2579	3.9	2.28	1.42-3.67	45	0.0006
Previous endocarditis	47/725	6.4	42/980	4.2	1.41	0.88-2.27	0	0.16
RVOT dysfunction								
Predominant PS	131/736	17.8	151/1754	8.6	1.89	0.90-3.98	81	0.09
Predominant PR	225/389	57.8	521/707	74.3	0.51	0.13-2.03	94	0.34
Both PS and PR	90/248		98/628		1.20	0.34-4.23	89	0.78

TPVR: Transcatheter pulmonary valve replacement; SPVR: Surgical pulmonary valve replacement; SD: Standard deviation; CI: Confidence interval; OR: Odds ratio; TGA: Transposition of great arteries; VSD: Ventricular septal defect; PS: Pulmonary stenosis; RVOT: Right ventricular outflow tract; PR: Pulmonary regurgitation.

**Table 3. Details of patients diagnosed with endocarditis in each study**

Study	Microorganisms		Treatment	
	TPVR	SPVR	TPVR	SPVR
Alassas et al. <sup>[9]</sup>	(n=6) 3 culture - 3 culture + (not specified)	None	5 treated medically (2 died) 1 treated surgically (SPVR)	None
Andresen et al. <sup>[10]</sup>	None	None	None	None
Caughron et al. <sup>[11]</sup>	None	None	None	None
Dilber et al. <sup>[12]</sup>	(n=1) <i>S. aureus</i>	None	1 treated surgically (SPVR)	None
Enezate et al. <sup>[13]</sup>	(n=3) Not specified	(n=25) Not specified	Not specified	Not specified
Georgiev et al. <sup>[14]</sup>	(n=18) Not specified	(n=6) Not specified	10 treated surgically 8 treated medically	4 treated surgically 2 treated medically
Grönning et al. <sup>[15]</sup>	(n=7) 1 <i>S. aureus</i> 2 <i>S. epidermidis</i> 1 <i>S. gordonii</i> 1 <i>S. pneumoniae</i> 1 <i>S. mitis</i> 1 <i>S. oralis</i>	(n=5) + 5 (Homograft* + Contegra**) *1 <i>P. acnes</i> 1 <i>S. epidermidis</i> 1 A. defective - <i>S. saprophyticus</i> 1 <i>H. parainfluenzae</i> 1 NA* 1 <i>C. albicans</i> 1 <i>S. sanguinis</i> - <i>R. rhodochrus</i> 1 <i>G. bergeri</i> 1 <i>S. epidermidis</i> 1 <i>S. aureus</i>	4 treated medically 3 treated surgically (2 PVR with homograft, 1 PVR with homograft and AVR with BAV)	Homograft: 2 treated medically + 1 treated medically 3 treated surgically (1 PVR with homograft and excision of VSD-patch, 2 PVR with homograft, Contegra: 4 treated surgically (1 PVR with Contegra, 2 PVR with homograft, 1 melody valve-in-valve)
Haas et al. <sup>[16]</sup>	(n=6) 4 <i>S. aureus</i> 1 <i>S. epidermidis</i> 1 <i>S. mitis/oralis</i>	(n=5) 2 <i>S. aureus</i> 1 <i>S. epidermidis</i> 1 <i>Streptococcus</i> + <i>Lactobacillus</i> 1 <i>Enterococcus</i>	6 treated medically	3 treated medically 1 treated surgically 1 died
Hribnik et al. <sup>[17]</sup>	(n=4) 1 <i>S. mitis</i> 1 <i>S. oralis</i> 1 <i>S. sanguinis</i> 1 HACEK	(n=4) <i>S. aureus</i> <i>S. epidermidis</i> <i>S. capitis</i>	3 treated surgically (SPVR)	4 treated surgically (Repeat PVR)
Lluri et al. <sup>[18]</sup>	(n=7) 1 culture - 4 <i>S. aureus</i> 1 <i>S. viridans</i> 1 <i>Abiotrophia/gramulicatella</i>	N: 2 1 culture - 1 <i>S. viridans</i>	5 treated medically 1 treated surgically 2 died	2 treated medically
Malekzadeh-Milani et al. <sup>[19]</sup>	Not specified (n=8)	Not specified (n=5)	Not specified	Not specified

**Table 3. Continued**

Study	Microorganisms		Treatment	
	TPVR	SPVR	TPVR	SPVR
O'Donnell et al. <sup>[20]</sup>	(n=4) 1 <i>S. aureus</i> 1 <i>S. epidermidis</i>	(n=4) 1 <i>S. aureus</i> 1 <i>Enterococcus</i>	1 treated medically 3 treated surgically	1 treated medically 3 treated surgically
Qu-Yang et al. <sup>[21]</sup>	1 coagulase - staphylococcus 1 <i>S. salivarius</i> (n=1) 1 <i>S. viridans</i> (n=6) Not specified	1 <i>A. actinomycetem-comitans</i> 1 <i>H. parainfluenzae</i> None None	1 treated medically	None
Sharma et al. <sup>[22]</sup>	Not specified	None	4 treated medically 2 treated surgically	None
Van Dijk et al. <sup>[23]</sup>	(n=8) 1 <i>S. aureus</i> 2 <i>S. viridans</i> 3 HACEK 1 <i>S. sanguinis</i> 1 <i>Corynebacterium pseudodiphtheriticum</i>	25 Not specified	6 treated medically 2 treated surgically	Not specified

TPVR: Transcatheter pulmonary valve replacement; SPVR: Surgical pulmonary valve replacement; PVR: Pulmonary valve replacement; AVR: Aortic valve replacement; BAV: Biological aortic valve; VSD: ventricular septal defect; NA: Not available.

valve replacement, 30 cases of IE would be prevented. A meta-regression of follow-up time on the incidence of IE was not statistically significant ( $p=0.753$ ), indicating the difference in follow-up times did not change the pooled risk of IE (Figure 3).

Overall mortality was reported in eleven comparison groups. Total mortality was similar between TPVR and SPVR (OR: 0.73, 95% CI: 0.43-1.25,  $p=0.25$ ) (Figure 4). Inclusion of only studies with a lower risk of bias did not alter the results with TPVR valves having similar total mortality to SPVR (OR: 0.76, 95% CI: 0.42-1.36,  $p=0.35$ ). The forest plot showed a low risk of bias and low heterogeneity ( $I^2=0\%$ ). Forest and Funnel plots and Egger's regression test results are reported in Supplemental Figures 2.

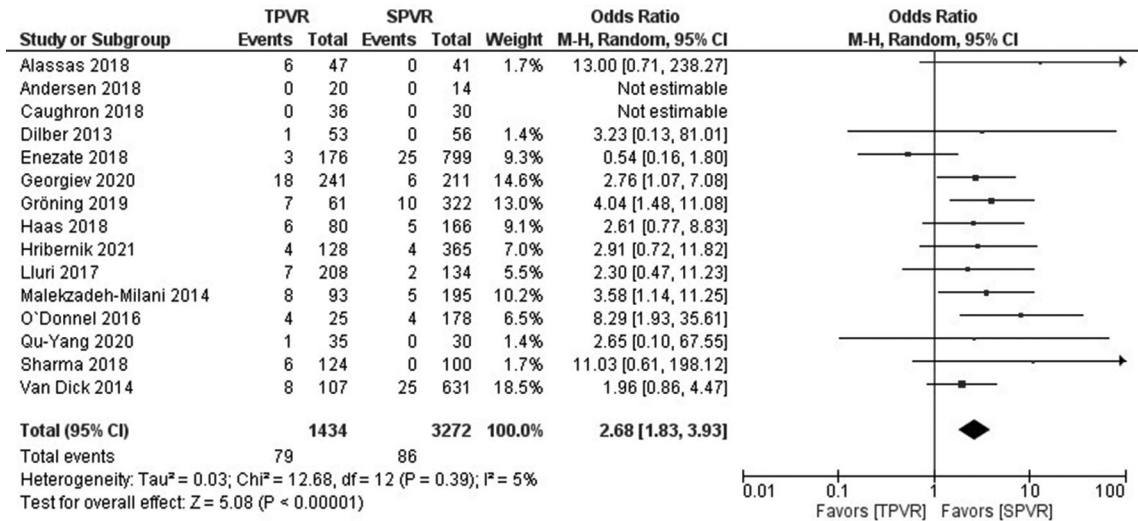
## DISCUSSION

After the first transcatheter valve implantation, Melody™ valve into a failing prosthetic conduit from the RV to the pulmonary artery, TPVR has become an attractive and widely used alternative to SPVR.<sup>[2]</sup> However, despite its significant advances in treating CHD, IE remains a major concern for the longer-term outcome.<sup>[25]</sup> Although a strong relationship between endocarditis and the Melody™ valve was reported in the literature, this is not specific to the Melody™ valve or bovine jugular vein-based prostheses in the RVOT due to IE was documented with other transcatheter valves and other implant locations.<sup>[26,27]</sup> The risk of IE with the Sapien™ valve (Edwards Lifesciences, Irvine, CA, USA), which has bovine pericardial tissue leaflets, even though still present, seems to be lower incidence rates than the Melody™ valve. However, given the shorter follow-up time, the Sapien™ has been in clinical use compared with Melody™ and surgical valves. Therefore, it was not surprising that this might cause a lower incidence rate of IE in the Sapien™ valve IE.<sup>[28,29]</sup>

The presented study evaluated the incidence of IE, the clinical features of the included studies, the patients' characteristics, and the overall mortality in TPVR and SPVR patients. Therefore, these data provide critical information for the literature to modify the risk/benefit ratio in individual bases to lead the patients according to the complexity of the prosthesis implantation way.

Based on the data reviewed in this analysis, there was clear evidence to suggest that IE after TPVR was more common than surgical implantation of the pulmonary valve (OR: 2.68, 95% CI: 1.83-3.93,  $p<0.00001$ ). This indicates that intervention methods



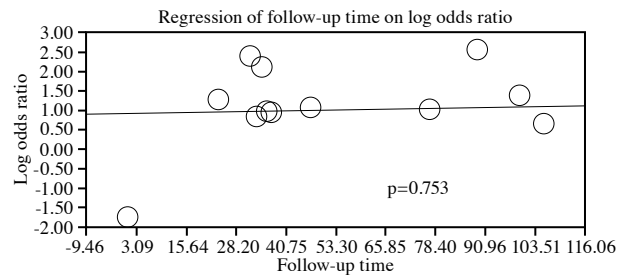


**Figure 2.** Forest displaying the OR's of infective endocarditis between TPVR and SPVR. The middle of the squares corresponds to the mean difference; horizontal lines show 95% CIs; middle of the filled diamond shows the pooled mean difference. Results of a test of heterogeneity between studies is given below the summary statistics.

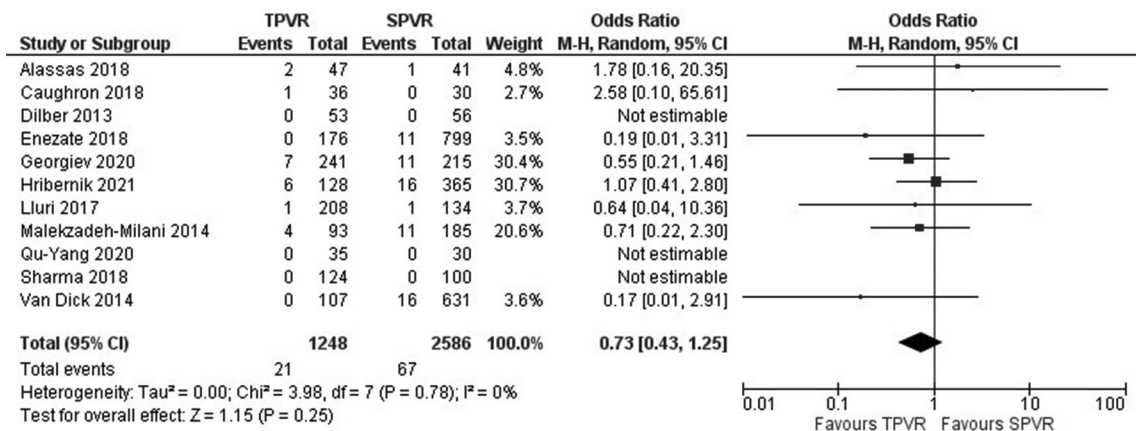
TPVR: Transcatheter pulmonary valve replacement; SPVR: Surgical pulmonary valve replacement; CIs: Confidence interval; OR: Odds ratio.

and specific tissue characteristics may be predisposed to subsequent bacterial infection. In addition, in the light of literature, there is a considerable risk and mortality burden of endocarditis in patients with CHD, particularly those with previously operated cyanotic or conotruncal anomalies such as tetralogy of Fallot, which was also the predominant CHD in this analysis (44% vs. 43% in TPVR vs. SPVR).<sup>[27,30]</sup>

It is well known that prior history of endocarditis may transmit the risk for future endocarditis.<sup>[31]</sup>



**Figure 3.** Meta-regression of follow-up time on log OR of infective endocarditis.



**Figure 4.** Forest plot displaying the OR's overall mortality between TPVR and SPVR. The middle of the squares corresponds to the mean difference; horizontal lines show 95% CIs; middle of the filled diamond shows the pooled mean difference. Results of a test of heterogeneity between studies is given below the summary statistics.

TPVR: Transcatheter pulmonary valve replacement; SPVR: Surgical pulmonary valve replacement; CI: Confidence interval; OR: Odds ratio.

However, since most of the studies have not routinely delineated endocarditis history with a statistical confirmation, these arise the question of whether patients with a history of endocarditis have any additional risk or other adverse outcomes after TPVR versus surgical replacement.<sup>[32]</sup> Nevertheless, in this meta-analysis, infectious complications in patients with a history of IE, TPVR and SPVR did not suggest significant differences, and that could not explain why the incidence of IE was different in the two groups. Nevertheless, it is worth reinforcing practices based on potential patient-related risk factors, including dental problems and skin or mucosal breakdown, to reduce the incidence rate of this complication. Moreover, our results are in accord with recent studies indicating that younger patients were at a higher risk of endocarditis (mean age of 21.6 years (95% CI: 19.2-24.0 years), which supports particular attention in educating pediatric/adolescent patients and their families about the importance of preventive measures.

There is also a growing body of literature indicating that the risk of IE is related more to the valve tissue (i.e., bovine jugular veins versus others) rather than the mode of valve implantation. The Contegra™ conduit and Melody™ valves, composed of the same biological substrate, demonstrate a significantly increased IE risk compared to other biological pulmonary valve substrates (i.e., homografts, Sapien™ valves, and Hancock™ valves).<sup>[16]</sup> This increased risk is attributed to their inherent asymmetry, altering flow dynamics. The resultant structural degeneration with high-velocity jets, coupled with thrombi on the prosthesis (non-bacterial thrombotic endocarditis), surface roughness, trauma due to the stent preparation, and implantation may serve as a nidus for the organisms to adhere prosthetic valve.<sup>[33,34]</sup> These findings further support the studies' suggestion that antiplatelet or anticoagulant therapy may reduce endocarditis risk, which merits consideration in the TPVR population.<sup>[19,35]</sup> However, there are currently no specific guideline recommendations for antiplatelet or anticoagulant therapy duration; the studies included in this meta-analysis are also limited by the lack of uniformity in the definition.

Patients with CHD regularly need reoperations for RVOT reconstruction after corrective or palliative operation in infancy or early childhood. Therefore, it was kept in mind that TPVR was preferred as an alternative for surgical treatment with much less morbidity than repeated surgery, albeit an association

of IE in these patients increases. Although mortality can reach up to 24% for native valve IE and exceeds 46% for prosthetic valve endocarditis,<sup>[36]</sup> total mortality was similar between TPVR and SPVR (OR: 0.73, 95% CI: 0.43-1.25,  $p=0.25$ ) in this analysis. Hence, TPVR in this group is still inspiring with procedural and long-term success rates.

We also attempted to evaluate the importance of follow-up time on the reported incidence of IE in this patient population. Although IE tended to occur earlier after TPVR than after SPVR,<sup>[9,10]</sup> the meta-regression of follow-up time on the incidence of IE, albeit positively correlated, was not statistically significant ( $p=0.753$ ) in the present analysis. This indicated that the difference in follow-up times did not change the pooled risk of IE.

This present analysis, although intended to be comprehensive, still bears limitations. First, it included observational studies, and no randomized controlled trials were available for inclusion at the study time. Additionally, much of the studies tend to be descriptive to identify the outcomes on the procedure's effectiveness, but have little insight into mechanisms or potential risk factors for endocarditis or its inconsistent sequelae. Finally, moderate heterogeneity was found concerning the included studies' results, as there were changing degrees of pre-procedural gradients and patient baseline CHD characteristics although leave-one-out analysis affirmed the consistency of the results.

In conclusion, transcatheter pulmonary valve replacement is a feasible alternative to surgical pulmonary valve replacement in selected patients with severe right ventricular outflow tract dysfunction. Moreover, it was associated with similar long-term mortality incidence rates as surgical pulmonary valve replacement. However, the higher incidence of IE in transcatheter pulmonary valve replacement compared to surgical valve options remains a significant concern, despite increased experience with the technique and technology. Hence, this requires further exploration and preventive strategies. Regarding this analysis, surgical treatment of right ventricular outflow tract dysfunction is still a viable option in patients with prohibitive risk. Nevertheless, the findings reported from well-conducted randomized controlled trials with real-world evidence addressing whether the relative risk differs significantly between transcatheter pulmonary valve replacement with the Melody™ valve, the Sapien™ valve, or other devices, or surgical replacement with various conduits or prostheses and later treatment strategies are warranted.

**Data Sharing Statement:** The data that support the findings of this study are available from the corresponding author upon reasonable request.

**Author Contributions:** Analyzed, collected and review the data: E.I.C.; Contributed to the design, review of literatures and interpretation: E.I.C., B.B, and L.Ç.O.; Wrote the manuscript: E.I.C.; Contributed to supervision, last editing and the critical review: A.C.; All authors contributed to the article and approved the submitted version.

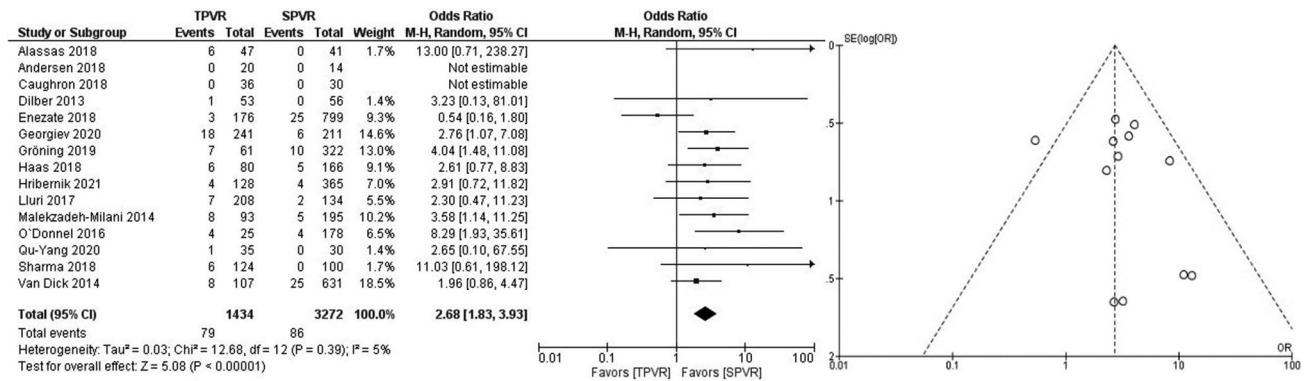
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## REFERENCES

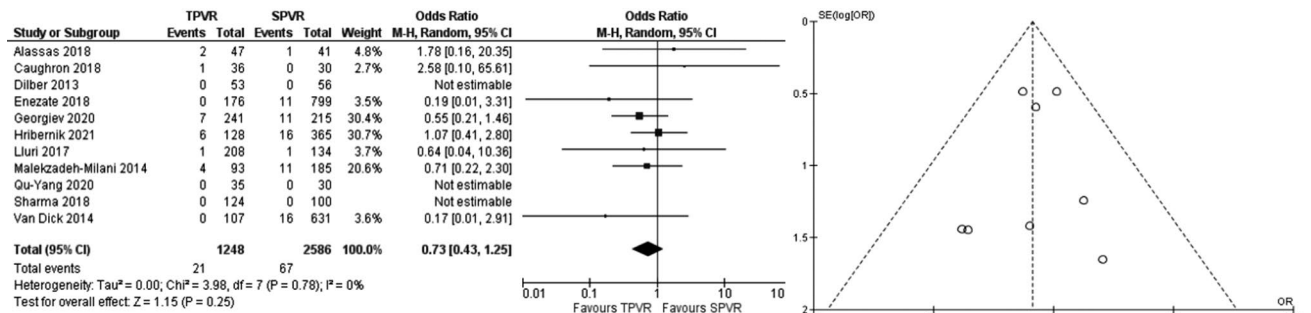
1. Levi DS, Sinha S, Salem MM, Aboulhosn JA. Transcatheter native pulmonary valve and tricuspid valve replacement with the sapien XT: Initial experience and development of a new delivery platform. *Catheter Cardiovasc Interv* 2016;88:434-43.
2. Bonhoeffer P, Boudjemline Y, Saliba Z, Merckx J, Aggoun Y, Bonnet D, et al. Percutaneous replacement of pulmonary valve in a right-ventricle to pulmonary-artery prosthetic conduit with valve dysfunction. *Lancet* 2000;356:1403-5.
3. Cheatham JP, Hellenbrand WE, Zahn EM, Jones TK, Berman DP, Vincent JA, et al. Clinical and hemodynamic outcomes up to 7 years after transcatheter pulmonary valve replacement in the US melody valve investigational device exemption trial. *Circulation* 2015;131:1960-70.
4. Andresen B, Mishra V, Lewandowska M, Andersen JG, Andersen MH, Lindberg H, et al. In-hospital cost comparison between percutaneous pulmonary valve implantation and surgery. *Eur J Cardiothorac Surg* 2017;51:747-53.
5. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. *Syst Rev* 2016;5:210.
6. Hupe M. EndNote X9. *J Electron Resour Med Libr* 2019;16:117-9.
7. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71.
8. Borenstein M, Hedges L, Higgins J, Rothstein H. *Comprehensive meta-analysis version 3*. Englewood, NJ, Biostat; 2013. Available at: <https://www.meta-analysis.com/downloads/Meta-Analysis%20Manual%20V3.pdf>
9. Alassas K, Mohty D, Clavel MA, Husain A, Hijji T, Aljoufan M, et al. Transcatheter versus surgical valve replacement for a failed pulmonary homograft in the Ross population. *J Thorac Cardiovasc Surg* 2018;155:1434-44.
10. Andresen B, Döhlen G, Diep LM, Lindberg H, Fosse E, Andersen MH. Psychosocial and clinical outcomes of percutaneous versus surgical pulmonary valve implantation. *Open Heart* 2018;5:e000758.
11. Caughron H, Kim D, Kamioka N, Lerakis S, Yousef A, Maini A, et al. Repeat pulmonary Valve replacement: Similar intermediate-term outcomes with surgical and transcatheter procedures. *JACC Cardiovasc Interv* 2018;11:2495-503.
12. Dilber D, Hörer J, Malcic I, Hess J, Ewert P, Eicken A. Percutaneous pulmonary valve implantation and surgical valve replacement in patients with right ventricular outflow tract dysfunction--a complementary treatment concept. *Int J Cardiol* 2013;169:e3-5.
13. Enezate T, Omran J, Bhatt DL. Percutaneous versus surgical pulmonic valve implantation for right ventricular outflow tract dysfunction. *Cardiovasc Revasc Med* 2019;20:553-8.
14. Georgiev S, Ewert P, Eicken A, Hager A, Hörer J, Cleuziou J, et al. 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.
15. Gröning M, Tahri NB, Søndergaard L, Helvind M, Ersbøll MK, Ørbæk Andersen H. 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.
16. Haas NA, Bach S, Vcasna R, Laser KT, Sandica E, Blanz U, et al. The risk of bacterial endocarditis after percutaneous and surgical biological pulmonary valve implantation. *Int J Cardiol* 2018;268:55-60.
17. Hribernik I, Thomson J, Ho A, English K, Van Doorn C, Jaber O, et al. Comparative analysis of surgical and percutaneous pulmonary valve implants over a 20-year period. *Eur J Cardiothorac Surg* 2022;61:572-9.
18. Lluri G, Levi DS, Miller E, Hageman A, Sinha S, Sadeghi S, et al. Incidence and outcome of infective endocarditis following percutaneous versus surgical pulmonary valve replacement. *Catheter Cardiovasc Interv* 2018;91:277-84.
19. Malekzadeh-Milani S, Houeijeh A, Jalal Z, Hascoet S, Bakloul M, Aldebert P, et al. French national survey on infective endocarditis and the Melody™ valve in percutaneous pulmonary valve implantation. *Arch Cardiovasc Dis* 2018;111:497-506.
20. O'Donnell C, Holloway R, Tilton E, Stirling J, Finucane K, Wilson N. Infective endocarditis following Melody valve implantation: Comparison with a surgical cohort. *Cardiol Young* 2017;27:294-301.
21. Ou-Yang WB, Qureshi S, Ge JB, Hu SS, Li SJ, Yang KM, et al. Multicenter comparison of percutaneous and surgical pulmonary valve replacement in large RVOT. *Ann Thorac Surg* 2020;110:980-7.
22. Sharma V, Griffiths ER, Eckhauser AW, Gray RG, Martin MH, Zhang C, et al. Pulmonary valve replacement: A single-institution comparison of surgical and transcatheter valves. *Ann Thorac Surg* 2018;106:807-13.
23. Van Dijk I, Budts W, Cools B, Eyskens B, Boshoff DE, Heying R, et al. Infective endocarditis of a transcatheter pulmonary valve in comparison with surgical implants. *Heart* 2015;101:788-93.
24. Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, et al; 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). *Eur Heart J* 2015;36:3075-128.
25. Khambadkone S, Coats L, Taylor A, Boudjemline Y, Derrick G, Tsang V, et al. Percutaneous pulmonary valve implantation in humans: Results in 59 consecutive patients. *Circulation* 2005;112:1189-97.

26. Valve ESXTH. with the NovaFlex+ Delivery System Instructions for Use. 2016. Available at: <https://www.edwards.com/gb/devices/heart-valves/transcatheter-sapien-xt>
27. Rushani D, Kaufman JS, Ionescu-Ittu R, Mackie AS, Pilote L, Therrien J, et al. Infective endocarditis in children with congenital heart disease: Cumulative incidence and predictors. *Circulation* 2013;128:1412-9.
28. Wilson WM, Benson LN, Osten MD, Shah A, Horlick EM. Transcatheter pulmonary valve replacement with the Edwards Sapien system: The Toronto experience. *JACC Cardiovasc Interv* 2015;8:1819-27.
29. Hascoet S, Mauri L, Claude C, Fournier E, Lourtet J, Riou JY, et al. Infective endocarditis risk after percutaneous pulmonary valve implantation with the melody and sapien valves. *JACC Cardiovasc Interv* 2017;10:510-7.
30. Kuijpers JM, Koolbergen DR, Groenink M, Peels KCH, Reichert CLA, Post MC, et al. Incidence, risk factors, and predictors of infective endocarditis in adult congenital heart disease: Focus on the use of prosthetic material. *Eur Heart J* 2017;38:2048-56.
31. Østergaard L, Valeur N, Ihlemann N, Bundgaard H, Gislason G, Torp-Pedersen C, et al. Incidence of infective endocarditis among patients considered at high risk. *Eur Heart J* 2018;39:623-9.
32. McElhinney DB. Reflection and rationalization: Making sense of the literature on endocarditis after transcatheter pulmonary valve replacement. *Circ Cardiovasc Interv* 2017;10:e004983.
33. Baltimore RS, Gewitz M, Baddour LM, Beerman LB, Jackson MA, Lockhart PB, et al. Infective endocarditis in childhood: 2015 update: A scientific statement from the American Heart Association. *Circulation* 2015;132:1487-515.
34. Hou S, Gu H, Smith C, Ren D. Microtopographic patterns affect *Escherichia coli* biofilm formation on poly (dimethylsiloxane) surfaces. *Langmuir* 2011;27:2686-91.
35. Schneider H, Vogt M, Boekenkamp R, Hoerer J, Eicken A, Foth R, et al. Melody transcatheter valve: Histopathology and clinical implications of nine explanted devices. *Int J Cardiol* 2015;189:124-31.
36. Cresti A, Chiavarelli M, Scalese M, Nencioni C, Valentini S, Guerrini F, et al. Epidemiological and mortality trends in infective endocarditis, a 17-year population-based prospective study. *Cardiovasc Diagn Ther* 2017;7:27-35.



**Supplemental Figure 1.** Forest displaying the OR's of infective endocarditis between TPVR and SPVR. Funnel plot of SE by logit odds ratio, for assessment of publication bias.

TPVR: Transcatheter pulmonary valve replacement; SPVR: Surgical pulmonary valve replacement; CI: Confidence interval; SE: Standard error; OR: Odds ratio.



**Supplemental Figure 2.** Forest plot displaying the OR's overall mortality between TPVR and SPVR. Funnel plot of SE by logit odds ratio, for assessment of publication bias.

TPVR: Transcatheter pulmonary valve replacement; SPVR: Surgical pulmonary valve replacement; CI: Confidence interval; SE: Standard error; OR: Odds ratio.