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Endocarditis After Transcatheter Pulmonary Valve Replacement

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ABSTRACT

BACKGROUND Endocarditis has emerged as one of the most concerning adverse outcomes in patients with congenital anomalies involving the right ventricular outflow tract (RVOT) and prosthetic valves.

OBJECTIVES The aim of this study was to evaluate rates and potential risk factors for endocarditis after transcatheter pulmonary valve replacement in the prospective Melody valve trials.

METHODS All patients in whom a transcatheter pulmonary valve (TPV) was implanted in the RVOT as part of 3 prospective multicenter studies comprised the analytic cohort. The diagnosis of endocarditis and involvement of the TPV were determined by the implanting investigator.

RESULTS A total of 309 patients underwent transcatheter pulmonary valve replacement (TPVR) and were discharged with a valve in place. The median follow-up duration was 5.1 years, and total observation until study exit was 1,660.3 patient-years. Endocarditis was diagnosed in 46 patients (median 3.1 years after TPVR), and a total of 35 patients were reported to have TPV-related endocarditis (34 at the initial diagnosis, 1 with a second episode). The annualized incidence rate of endocarditis was 3.1% per patient-year and of TPV-related endocarditis was 2.4% per patient-year. At 5 years post-TPVR, freedom from a diagnosis of endocarditis was 89% and freedom from TPV-related endocarditis was 92%. By multivariable analysis, age ≤12 years at implant (hazard ratio: 2.3; 95% confidence interval: 1.2 to 4.4; $p = 0.011$) and immediate post-implant peak gradient ≥15 mm Hg (2.7; 95% confidence interval: 1.4 to 4.9; $p = 0.002$) were associated with development of endocarditis and with development of TPV-related endocarditis (age ≤12 years: 2.8; 95% confidence interval: 1.3 to 5.7; $p = 0.006$; gradient ≥15 mm Hg: 2.6; 95% confidence interval: 1.3 to 5.2; $p = 0.008$).

CONCLUSIONS Endocarditis is an important adverse outcome following TVPR in children and adults with postoperative congenital heart disease involving the RVOT. Ongoing efforts to understand, prevent, and optimize management of this complication are paramount in making the best use of TPV therapy. (Melody Transcatheter Pulmonary Valve [TPV] Study: Post Approval Study of the Original Investigational Device Exemption [IDE] Cohort; NCT00740870; Melody Transcatheter Pulmonary Valve Post-Approval Study; NCT01186692; and Melody Transcatheter Pulmonary Valve [TPV] Post-Market Surveillance Study; NCT00688571) (J Am Coll Cardiol 2018;72:2717–28)

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ABBREVIATIONS AND ACRONYMS

CHD = congenital heart disease

RVOT = right ventricular outflow tract

TPV = transcatheter pulmonary valve

TPVR = transcatheter pulmonary valve replacement

Bonhoeffer et al. (1) initially described transcatheter pulmonary valve replacement (TPVR) for right ventricular outflow tract conduit dysfunction in the year 2000. Five years later, they first reported endocarditis in a patient who had undergone TPVR (2). Subsequently, a number of studies and case reports have focused on this issue (3–11), as discussed in a recent review (12). The largest prior study to report the incidence and assess risk factors for endocarditis after TPVR was a pooled analysis of data from the 3 prospective multicenter valve trials in the United States, Canada, and Europe, which was based on data collected through mid-2012 and published in 2013 (4). Since then, substantial additional follow-up has accumulated in all 3 trials, and additional single-center or multicenter studies have been reported, adding to the discussion about endocarditis after TPVR (7–10). Endocarditis has also emerged as an important adverse outcome after transcatheter aortic valve replacement (13,14). To advance our insight into the incidence and outcomes of endocarditis after TPVR, and to evaluate potential risk factors for this time-related adverse event, we updated and expanded the analysis of data from the prospective multicenter valve trials.

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METHODS

STUDY SUBJECTS AND PROTOCOLS. Similar to our prior report (4), this study included all patients in whom a Melody TPV (Medtronic, Dublin, Ireland) was implanted with a conduit or bioprosthetic valve in the pulmonary position as part of 3 Medtronic-sponsored prospective multicenter studies: 1) the Post-Approval Study of the original U.S. IDE (Investigational Device Exemption) cohort; 2) the U.S. PAS (Post-Approval Study); and 3) the Melody TPV PMSS (Post-Market Surveillance Study) in Europe and Canada. Details of these trials were summarized previously (4,15–19). Patients were followed until study exit: the earliest of death, TPV explant, or completion of the prescribed follow-up duration (10 years IDE, 5 years for PAS and PMSS). The databases were locked for this study on November 18, 2016 (IDE and PAS), and September 29, 2015 (PMSS).

DEFINITION AND ASCERTAINMENT OF ENDOCARDITIS CASES. Patients who developed endocarditis were ascertained from the prospective study databases maintained by Medtronic, as summarized previously (4). The diagnosis of endocarditis and involvement of the TPV were determined by the implanting investigator. Two adverse event codes for endocarditis were used: "endocarditis," which was intended to reflect TPV-related endocarditis, and "endocarditis other than TPV." "Endocarditis" was defined as "any infection involving the Melody TPV that meets the criteria for definite endocarditis according to the modified Duke Criteria," with the modified Duke criteria enumerated (20). "Endocarditis other than TPV" was not specifically defined. Additional details related to definition and ascertainment of endocarditis cases are presented in the Online Appendix. In addition to these definitions, objective evidence of TPV involvement was determined from data collected in the supplemental survey (see the Online Appendix): evidence of vegetations on the TPV by imaging, surgical inspection, or pathological evaluation, or the presence of new or progressive TPV dysfunction (moderate or severe PR, new onset or progression of gradient to >60 mm Hg, catheter-based intervention for obstruction).

TPV-ENDOCARDITIS CLINICAL CLASSIFICATION SCHEME. To better understand and more effectively manage TPVR-associated endocarditis, a clinical categorization scheme was developed based on the published data and collective experience treating this condition, a priori to analysis of the results of this study. The critical distinguishing features of this system are: 1) clinical severity of the presentation; 2) involvement of the TPV; 3) clinical response to initial antibiotic therapy; and 4) presence of factors

as a consultant for Medtronic. Dr. Balzer is a proctor for Medtronic and Abbott Vascular; and has served as a Principal Investigator for Medtronic. Dr. Lung is an employee and shareholder of Medtronic. Dr. Zahn has served as a proctor and consultant for Medtronic, Edwards Lifesciences, and Abbott Vascular; is the national Principal Investigator for the Edwards Lifesciences Alterra Study; and is the national Principal Investigator for the Abbott Vascular ADO II-AS Study. Dr. Hellenbrand has served as a proctor and consultant for Medtronic; and has served as a proctor for Edwards Lifesciences. Dr. Kreutzer has received research support from Medtronic and Edwards Lifesciences; and has served as a consultant for Medtronic. Dr. Eicken has served as a proctor for Medtronic. Dr. Jones has received research support from Medtronic and Edwards Lifesciences; and has served as a consultant and scientific advisory board member for Medtronic. Prof. Ewert is a proctor for the Melody valve (Medtronic) and for the Sapien Pulmonic valve (Edwards Lifesciences). All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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TABLE 1 Proposed Clinical Classification System for Endocarditis After TPVR and Distribution of Patients and Outcomes According to Schematic Categories

		A	B	C
Clinical Severity Category	**TPV Involvement**	**Definite TPV Involvement**	**No Evidence of TPV Involvement With Good Noninvasive Imaging**	**TPV Involvement Cannot Be Determined Definitively With Noninvasive Evaluation**
1 (n = 21)*	Not severe Symptomatic improvement with antibiotics	Total: 9 Died: 0 (0%) Explanted: 1 (11%) Any TPV reintervention†: 2 (22%)	Total: 7 Died: 0 (0%) Explanted: 0 (0%) Any TPV reintervention†: 1 (14%)	Total: 3 Died: 0 (0%) Explanted: 1 (33%) Any TPV reintervention†: 1 (33%)
2 (n = 9)‡	Intermediate Not severe but persistent/recurrent symptoms on antibiotics	Total: 8 Died: 1 (13%) Explanted: 5 (63%) Any TPV reintervention†: 7 (88%)	–	–
3 (n = 16)§	Severe Sepsis, shock, end-organ dysfunction, RV dysfunction, severe RVOT obstruction	Total: 10 Died: 0 (0%) Explanted: 7 (70%) Any TPV reintervention†: 8 (80%)	Total: 4 Died: 1 (25%) Explanted: 0 (0%) Any TPV reintervention†: 0 (0%)	Total: 1 Died: 1 (100%) Explanted: 1 (100%) Any TPV reintervention†: 1 (100%)

*2 patients in category 1 were undefined by alphanumeric group (and without death, explant, or reintervention), such that there were 21 total patients in category 1. †Any TPV reintervention refers to surgical or transcatheter pulmonary valve reintervention. ‡1 patient in category 2 died, and was undefined by alphanumeric group, such that there were 9 total patients in category 2. §1 patient in category 3 died, and was undefined by alphanumeric group, such that there were 16 total patients in category 3. TPV = transcatheter pulmonary valve; TPVR = transcatheter pulmonary valve replacement.

that may mitigate decision-making around management. Patients fit into 1 of 9 groups based on the first 3 of these features, with alphanumeric categorization based on clinical severity and response to antibiotics (numeric score) and TPV involvement (alpha grade) (Table 1).

DATA ANALYSIS. Data were presented as frequency or median (minimum to maximum, or quartile [Q] 1, Q3). Between-group comparisons of categorical and continuous data were performed using the Fisher exact test or the Wilcoxon rank sum test. The incidence of endocarditis (and TPV-related endocarditis) was calculated as an annualized event rate (% per patient-year) using the total patient follow-up until death, TPV explant, or most recent evaluation under the study protocol, including both initial and any recurrent episodes of IE as events. An annualized rate for first endocarditis episodes was calculated in a similar manner, including only initial episodes as events and truncating follow-up at the time of the initial endocarditis diagnosis. Kaplan-Meier curves were used to depict time-related freedom from endocarditis after TPVR. Analysis of potential risk factors for endocarditis was performed with Cox proportional hazards regression. Hazard ratios (HRs) and incidence rates were presented with 95% confidence intervals (CIs). Incidence rates were compared between groups with incidence rate ratios, and 95% CIs were calculated by assuming a Poisson model and considering the logarithm of the ratio. The SE was estimated in a logistical model, and a Ward 95% CI was calculated. Due to small numbers of implants within the trial at many centers, trial sites were combined into groups (i.e., by trial or number of implants) and incidence rate ratios were calculated. The goal of these analyses was not necessarily to determine if the different trials or high/low volume centers were at different risk, but rather to ascertain more generally whether there was any significant variation between centers.

RESULTS

INCIDENCE OF AND RISK FACTORS FOR ENDOCARDITIS. A total of 309 patients underwent TPVR and were discharged with a valve in place in the IDE (n = 148), PAS (n = 99), and PMSS (n = 62) trials. The median duration of follow-up was 5.1 years (Q1, Q3: 4.2, 7.0 years) and total observation until study exit was 1,660.3 patient-years (1,594.9 patient-years until first endocarditis diagnosis, most recent follow-up, or study exit). Endocarditis was diagnosed in 46 patients, a median of 3.1 years after TPVR (Q1, Q3: 1.4, 5.1 years), and a total of 35 patients were reported by the investigator to have TPV-related endocarditis (34 at the initial diagnosis; 1 with a second episode, as detailed in the following text). None of these cases were originally coded as sepsis or other infection. Patient and procedural data are summarized in Table 2, and clinical details at the time of presentation with endocarditis are summarized in Table 3. Among patients whose first endocarditis episode was classified as TPV-related by the implanting physician, 8 of 34 (24%) did not have objective evidence documenting involvement of the TPV but were coded as TPV-related by the respective implanters based on the determination that the endocarditis was related to the device. A total of 4 of 12 (33%) patients who were classified as not TPV-related were

TABLE 2 Demographic, Diagnostic, and Procedural Variables in Study Patients Who Did and Did Not Develop Endocarditis After TPVR With the Melody Valve (N = 309)

	Total (N = 309)	Any Endocarditis (n = 46)	TPV-Related Endocarditis (n = 35)	No Endocarditis (n = 263)	Any Endocarditis HR (95% CI)	Any Endocarditis* p Value	TPV-Related Endocarditis HR (95% CI)	TPV-Related Endocarditis* p Value
Age, yrs	18 (7–59)	16 (8–45)	15 (8–45)	19 (7–59)	0.99 (0.96–1.02)	0.47	0.97 (0.93–1.01)	0.12
Age group (reference >12 yrs)					2.23 (1.17–4.24)	0.015	2.62 (1.28–5.35)	0.008
Children ≤12 yrs	49 (16)	13 (28)	11 (31)	36 (14)				
Adolescents 13–18 yrs	107 (35)	14 (30)	10 (29)	93 (35)				
Young adults 19–29 yrs	96 (31)	10 (22)	9 (26)	86 (33)				
Older adults ≥30 yrs	57 (18)	9 (20)	5 (14)	48 (18)				
Male	205 (66)	33 (72)	23 (66)	172 (65)	1.37 (0.72–2.61)	0.33	1.00 (0.50–2.02)	0.99
No. of prior open-heart surgeries	2 (1–8)	2 (1–8)	2 (1–5)	2 (1–8)	1.01 (0.77–1.34)	0.93	0.81 (0.57–1.17)	0.27
Total # of surgical RVOT conduits	1 (0–5)	1 (1–3)	1 (1–3)	1 (0–5)	0.87 (0.59–1.28)	0.49	0.76 (0.48–1.22)	0.26
Age at first surgical conduit, yrs	4 (0–45)	5 (0–37)	3 (0–28)	4 (0–45)	0.99 (0.95–1.02)	0.45	0.97 (0.92–1.02)	0.19
Conduit type					1.00 (0.52–1.93)	1.00	0.82 (0.37–1.81)	0.63
Homograft (reference)	223 (72)	34 (74)	27 (77)	189 (72)				
Stented BPV	55 (18)	7 (15)	6 (17)	48 (18)				
Stented BPV conduit	25/55 (46)	4/7 (57)	4/6 (67)	21/48 (44)				
Stented BPV without conduit	30/55 (55)	3/7 (43)	2/6 (33)	27/48 (56)				
Nonvalved synthetic tube	10 (3)	3 (7)	1 (3)	7 (3)				
Contegra	13 (4)	2 (4)	1 (3)	11 (4)				
Other stentless biological conduit	8 (3)	0 (0)	0 (0)	8 (3)				
Implant duration of current conduit, yrs	9.7 (0.1–37.2)	9.8 (0.3–33.3)	10.1 (0.7–33.3)	9.6 (0.1–37.2)	1.01 (0.97–1.06)	0.54	1.02 (0.97–1.07)	0.40
Primary indication for TPVR					0.99 (0.56–1.77)	0.98	0.98 (0.50–1.92)	0.96
Stenosis	82 (26.5)	9 (20)	5 (14)	73 (28)				
Regurgitation (reference)	147 (47.6)	23 (50)	18 (51)	124 (47)				
Mixed	80 (25.9)	14 (30)	12 (34)	66 (25)				
Implanted RVOT conduit diameter, mm	21 (11–31)	21 (16–26)	20 (16–25)	21 (11–31)	0.93 (0.85–1.03)	0.18	0.91 (0.81–1.02)	0.10
Angiographic conduit diameter, mm	13.1 (4.5–23.1)	13.4 (6.0–20.1)	13.4 (6.0–20.1)	13.0 (4.5–23.1)	1.01 (0.92–1.10)	0.89	1.01 (0.91–1.11)	0.92
Delivery system size					0.81 (0.36–1.84)	0.62	0.79 (0.32–1.97)	0.62
18 mm (reference)	34 (11)	7 (15)	6 (17)	27 (10)				
20 mm	96 (31)	13 (28)	11 (31)	83 (32)				
22 mm	179 (58)	26 (57)	18 (51)	153 (58)				
Pre-stent implanted					1.00 (0.49–2.04)	0.99	1.00 (0.45–2.26)	0.99
None (reference)	255 (83)	36 (78)	27 (77)	219 (83)				
Single	36 (12)	6 (13)	6 (17)	30 (11)				
Multiple	18 (6)	4 (9)	2 (6)	14 (5)				
Valve post-dilated after implant	138 (45)	20 (44)	15 (43)	118 (45)	0.94 (0.52–1.69)	0.84	0.89 (0.45–1.75)	0.74
RVOT gradient, mm Hg†								
Pre-implant peak gradient	37 (2–110)	42 (17–78)	36 (17–63)	37 (2–110)	1.02 (1.00–1.04)	0.043	1.01 (0.99–1.03)	0.52
Post-implant peak gradient	14 (0–37)	16 (0–37)	16 (0–31)	13 (0–35)	1.07 (1.03–1.11)	0.001	1.04 (0.99–1.09)	0.12
Post-implant peak gradient ≥15 mm Hg	126 (42)	29 (64)	22 (65)	97 (38)	2.59 (1.42–4.71)	0.002	2.46 (1.23–4.89)	0.011
Pre-implant Doppler mean gradient	35 (5–97)	36 (11–63)	35 (11–63)	35 (5–97)	1.02 (1.00–1.05)	0.034	1.02 (1.00–1.05)	0.10
Discharge mean Doppler gradient	17 (3–54)	17 (6–36)	16 (6–36)	17 (3–54)	1.02 (0.98–1.06)	0.29	1.01 (0.97–1.05)	0.68

Values are median (minimum–maximum), n (%), or n/N (%), unless otherwise indicated. Hazard ratios reported are from univariate analysis. *Any endocarditis was analyzed in comparison to no endocarditis, and "TPV-related endocarditis" was compared with no TPV-related endocarditis. †Peak gradients refer to direct invasive measurements in the catheterization laboratory.

BPV = bioprosthetic valve; RVOT = right ventricular outflow tract; TPVR = transcatheter pulmonary valve; TPVR = transcatheter pulmonary valve replacement.

conservatively determined from the supplementary survey to have evidence of TPV involvement: 2 of these 4 had a new high gradient across the TPV, which was not specified in the adverse event code definition as a criterion for TPV involvement; in the other 2, there was a likely vegetation in the proximal pulmonary outflow tract that was considered to be strongly suggestive of TPV involvement even though it was not clearly associated with the TPV. In addition to transthoracic echocardiography, transesophageal imaging was reportedly used in 18 patients, but the valve was only visualized well in 5 of them; vegetations were identified by some method in 4 of the patients whose valve was not seen well and 1 whose was. Intracardiac echocardiography was used in 3 patients who also had transesophageal echocardiography, 2 of whom had vegetations associated with the TPV.

Infectious organisms are summarized in Table 4. Staphylococcal species were most common (43%), followed by Viridans group streptococcal species (37%). Five patients had a known prior history of endocarditis (3 with different organisms), and 24 of 46 (52%) had some type of predisposing or mitigating condition, including dental procedures, cutaneous wounds or infections, and infection involving other intracardiac foreign material (Table 4). Three patients (all with Staph aureus) had septic pulmonary embolism documented by computed tomography (the total number of patients evaluated with computed tomography was not available).

The annualized incidence rate of endocarditis was 3.1% per patient-year (3.1 cases per 100 patient-years) and of TPV-related endocarditis was 2.4% per patient-year. Estimated freedom from a diagnosis of endocarditis was 97% (95% CI: 96% to 99%) at 1 year and 89% (95% CI: 85% to 93%) at 5 years; freedom from TPV-related endocarditis was 97% at 1 year and 92% (95% CI: 89% to 95%) at 5 years (Central Illustration). When patients were analyzed according to objective evidence of TPV involvement rather than the investigator-determined adverse event code, freedom from endocarditis involving the valve was 99% (95% CI: 97% to 100%) at 1 year and 94% (95% CI: 92% to 97%) at 5 years. Competing outcomes, including endocarditis, death without endocarditis, and TPV explant without death or endocarditis, are depicted in Figure 1. Factors associated with any endocarditis or TPV-related endocarditis by univariable Cox regression are summarized in Table 2. In addition, post-TPVR mean Doppler RVOT gradient, treated as a time-varying covariate, was significantly associated with endocarditis risk (HR: 1.03 per mm Hg; 95% CI: 1.00 to 1.06; $p = 0.028$). By multivariable analysis, age ≤12 years of age at implant (HR: 2.3; 95% CI: 1.2 to 4.4; $p = 0.011$) and invasively measured post-implant peak gradient ≥15 mm Hg (HR: 2.7; 95% CI: 1.4 to 4.9; $p = 0.002$) were associated with development of any endocarditis, and with development of TPV-related endocarditis (age ≤12 years HR: 2.8; 95% CI: 1.3 to 5.7; $p = 0.006$; gradient ≥15 mm Hg HR: 2.6; 95% CI: 1.3 to 5.2; $p = 0.008$).

There were considerable differences in endocarditis incidence rates among study centers. Trial centers performed anywhere from 2 to 41 implants (median 15 implants) and reported 0 to 10 patients (median 1.5 patients) who developed endocarditis during 5.4 to 253.1 patient-years of follow-up (median 60.1 patient-years). The overall incidence rate ranged from 0 to 11.0 ($p = 0.20$). Outcomes according to center-related stratification are summarized in Table 5, and additional details are provided in the Online Appendix.

TABLE 3 Clinical Details and Extenuating Circumstances in Patients Diagnosed With Endocarditis

Clinical details associated with endocarditis presentation	
Documented evidence of TPV involvement	27
Vegetations on the TPV leaflets or device	18
With new significant RVOT obstruction	9
Also with moderate or severe PR	2
Without significant new RVOT obstruction	3
Also with moderate or severe PR	1
Data on RVOT obstruction data not reported	6
New moderate or severe RVOT obstruction without vegetations	9
Hemodynamic instability or septic syndrome	16
Known TPV stent fracture*	12
TPV stenosis before endocarditis diagnosis (mean Doppler gradient >30 mm Hg)*	11
Prior redo TPVR for stent fracture	3
Extenuating circumstances or risk factors for endocarditis†	
Cutaneous (skin or oral) lesions/infection‡	9
Other infections§	8
Prior history of endocarditis before TPVR	5
Concurrent endocarditis of other cardiac structures/devices‖	5
Known intravenous drug use	3
Dental cleaning or oral instrumentation directly preceding episode	1
Indwelling central line/dialysis catheter	1

Values are n. These data are for first (not recurrent) post-TPVR endocarditis episodes. *Four of these patients had both stenosis and a stent fracture, and 3 had undergone redo TPVR and the second valve was without stenosis or stent fracture prior to the endocarditis diagnosis. †Five patients had "none" entered for this item, and 17 had "unknown" or no information entered. ‡Cochlear implant site excoriation, oral ulcers, oropharyngeal trauma from endoscopy, hand laceration, acne, pacemaker pocket incision breakdown and infection, recent tattoo, not specified (n = 2). §Pneumonia (n = 3), infected hemodialysis catheter, sinusitis and otitis, sinusitis and cellulitis, Streptococcal pharyngitis, upper respiratory infection, not specified. ‖Aortic valve (n = 2), rhythm device leads (n = 2), ventricular septal defect patch (also aortic valve), tricuspid valve. Three of these patients also had TPV vegetations visualized and 1 had significant new RVOT obstruction.

PR = pulmonary regurgitation; other abbreviations as in Table 2.

TREATMENT AND OUTCOMES OF ENDOCARDITIS. All patients with endocarditis were treated with antibiotics except for 2, who died before treatment could be initiated. Interventions in patients with TPV- and non-TPV-related endocarditis are summarized in Figure 2, with further details in the Online Appendix. Patients ≤12 years of age at implant who developed endocarditis were significantly more likely to undergo TPV explant and conduit replacement than patients who were older (62% vs. 21%; $p = 0.012$).

A total of 5 patients died as a result of the infectious episode at 0, 4, 11, 37, and 63 days after diagnosis of endocarditis; 4 had a septic syndrome and 1 had pulmonary embolus. Two other patients with non-TPV-related endocarditis died 4 and 11 months later, unrelated to the endocarditis episode. A total of 4 of these 5 patients had staphylococcal infection (the other died soon after presentation and no organism was confirmed), and only 2 had evidence of TPV involvement. One of the 5 deaths was in a patient who was age ≤12 years at TPVR, and younger patients with endocarditis were no more likely to die than older patients ($p = 0.56$).

TABLE 4 Organisms and Selected Demographic, Clinical, and Outcome-Related Details Related to First Episode of Endocarditis

	Staph aureus* (n = 14)	VGS (n = 17)	Coagulase-Negative Staph (n = 6)	HACEK (n = 3)	Nutritionally Variant Strep (n = 2)	Culture-Negative or Unknown (n = 4)
TPV-related/TPV involvement*	10 (71)/9 (64)†	14 (82)/11 (65)†	3 (50)/2 (33)	3 (100)/1 (33)†	1 (50)/2 (100)	4 (100)/2 (50)†
Significant RVOT obstruction‡	5 (36)	7 (41)	2 (33)	1 (33)	1 (50)	1 (25)
Died	3 (21)	0 (0)	1 (17)	0 (0)	0 (0)	1 (25)
Explanted	6 (43)	4 (24)	0 (0)	1 (33)	2 (100)	2 (50)
Age at TPVR, yrs	17 (11–45)	20 (10–39)	24 (10–44)	9 (8–12)	11 (11–11)	14 (10–20)
Duration from TPVR to endocarditis						
<1 yr	3 (21)	2 (12)	1 (17)	1 (33)	0 (0)	1 (25)
>4 yrs	4 (29)	6 (35)	4 (67)	0 (0)	2 (100)	3 (75)
Prior history of endocarditis§	4 (29)/2 (14)	0 (0)	1 (1)/0 (0)	0 (0)	0 (0)	0 (0)
Concurrent risk factor	10 (71)	6 (35)	3 (50)	1 (33)	1 (50)	3 (75)

Values are n (%) of column total or median (minimum–maximum). *Event coded as TPV-related/evidence of TPV involvement reported on supplemental event form. †Data on TPV involvement not available for 1 patient in these groups. ‡New or progressive in severity compared to pre-endocarditis. §Total number/known to be with same organism.

HACEK = Haemophilus species, Aggregatibacter species, Cardiobacterium hominis, Eikenella corrodens, and Kingella species; VGS = viridans group Streptococcal species; other abbreviations as in Table 2.

Among the 27 patients who survived the first endocarditis episode with the original valve in place, the median follow-up after the endocarditis diagnosis was 2.1 years. Of these patients, 6 (4 with TPV-related and 2 with non-TPV-related endocarditis on the first episode) developed a second episode of endocarditis 0 to 4 years after the first, with the same organism in 2 patients and a different organism in 4. Three of these 6 patients were active intravenous drug users. Freedom from recurrent endocarditis was 78% (95% CI: 58% to 98%) 3 years after the first episode. Two of the 6 patients with recurrent endocarditis had been treated with a transcatheter procedure after the first endocarditis episode (1 angioplasty for obstruction, 1 redo TPVR for obstruction associated with stent fractures), and the others had been managed medically. All 6 of these patients survived after the recurrent endocarditis; 4 underwent explant and the other 2 remained free from further infection 0.2 and 3.2 years after the second episode.

TPV-ENDOCARDITIS CLINICAL CLASSIFICATION SCHEME. It was possible to assign a numeric endocarditis severity grade to all patients, but classification of TPV involvement (alpha group) could not be determined in 4 due to incomplete data. Additional details are provided in Table 1 and the Online Appendix.

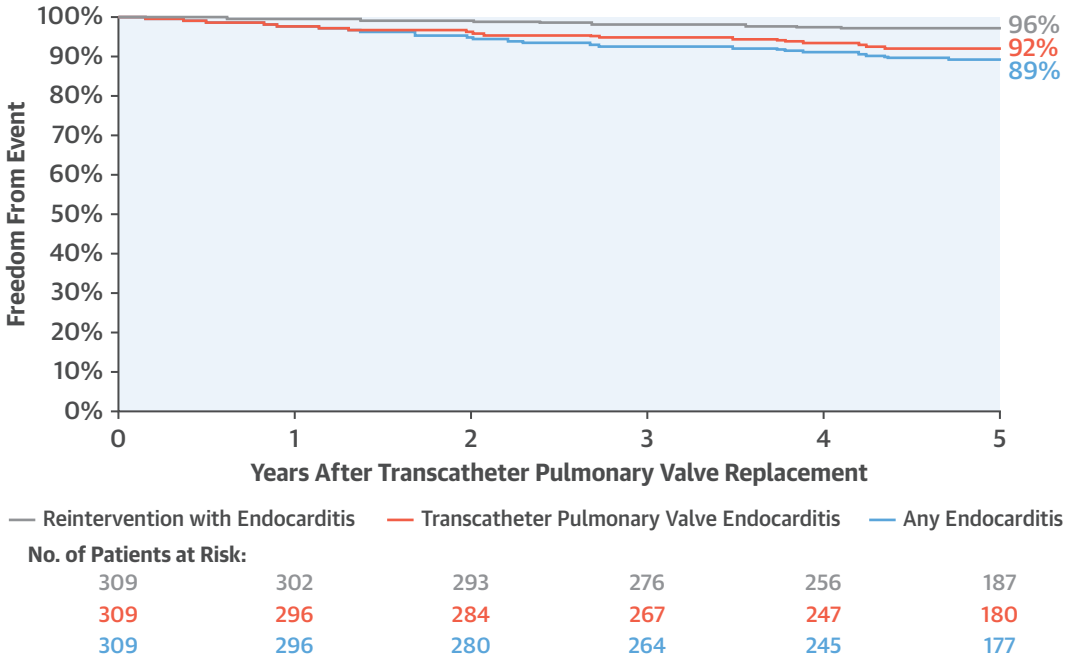
DISCUSSION

RISK OF ENDOCARDITIS AFTER TPVR IN PATIENTS WITH CHD. On the background of growing published data around transcatheter valve therapies and endocarditis (3-14,21), this large study of a prospectively followed cohort with over 1,600 years of post-TPVR evaluation contributes several important insights. Notably, the risk of endocarditis after TPVR persisted through the 5-year follow-up period. This finding is not surprising, and was also reflected in the much smaller investigational study of TPVR using the Sapien valve (Edwards Lifesciences, Irvine, California), which documented cases at least 4 years after implant (21). We also noted variability in endocarditis incidence rates among study centers, suggesting that random or center-related factors may be relevant determinants of risk, although lack of detailed data precluded further insight into these differences. A subset of patients presented with or developed severe RVOT obstruction sometimes with a clinically extreme presentation, a manifestation that was not specific to a particular organism or patient profile.

Multivariable analysis revealed higher post-TPVR RVOT gradient and younger age at implant to be risk factors for endocarditis. RVOT stenosis was previously associated with higher endocarditis risk (4,5), but an association with younger age has not been reported. Although a residual peak gradient of 15 mm Hg may seem modest, patients with obstructed RVOT conduits frequently manifest much higher gradients during exercise, even after TPVR with a good result, such that the gradient observed in the catheterization laboratory may not always reflect the true afterload burden (22). Regardless, this finding supports aggressive pre-dilation, pre-stenting, and post-dilation to achieve maximum relief of RVOT obstruction at the time of TPVR, taking into account potential complications such as coronary compression and conduit rupture.

Other predisposing conditions or risk factors, including a history of endocarditis and temporally related dental work or cutaneous infections, were relatively common in prior reports (12), and such

CENTRAL ILLUSTRATION **Freedom From Endocarditis After Transcatheter Pulmonary Valve Replacement**



McElhinney, D.B. et al. J Am Coll Cardiol. 2018;72(22):2717–28.

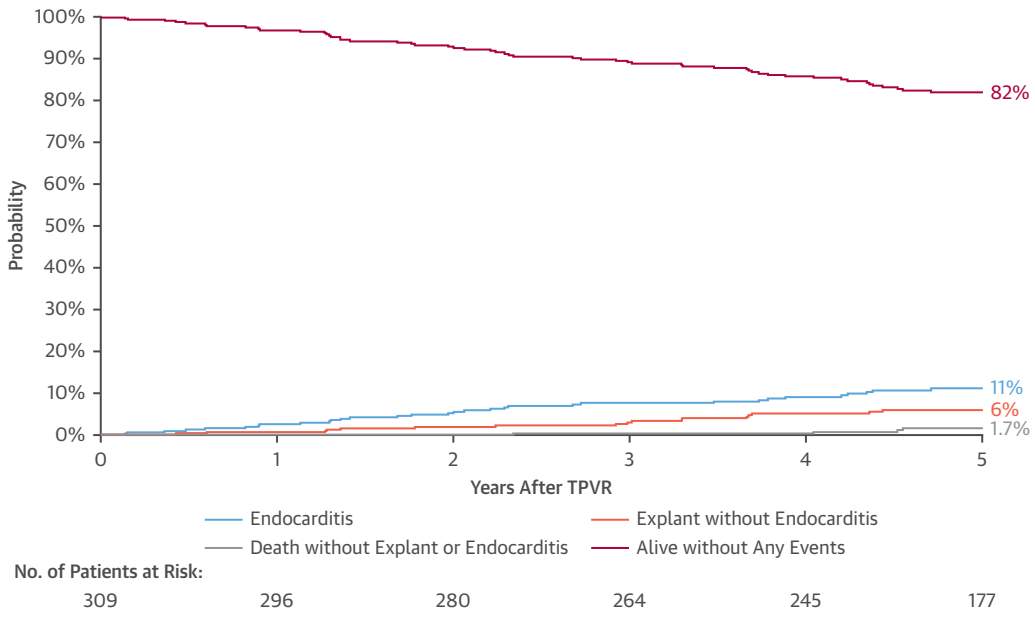
The Kaplan-Meier curves depict freedom from any endocarditis **(blue line)** (89% at 5 years [95% CI: 85% to 93%]), freedom from transcatheter pulmonary valve-related endocarditis **(orange line)** (92% at 5 years [95% CI: 89% to 95%]), and freedom from reintervention with endocarditis **(gray line)** (96% at 5 years [95% CI: 94% to 99%]).

factors were reported in 52% of endocarditis cases in this series. However, due to the challenges in estimating their prevalence among the entire cohort, we could not assess the risk associated with such factors. Similarly, as in prior reports, there were important confounding factors in many cases, such as aortic valve involvement or infection of other intracardiac foreign material, making it difficult to assess the burden of endocarditis related to TPVR per se (12,23). Thus, regardless of RVOT- or TPV-related variables, it is clear that potentially modifiable patient-related factors are critical in determining endocarditis risk.

The background risk of endocarditis in this patient population has not been well characterized until recently. Several recent studies highlighted the considerable and ongoing risk and mortality burden of endocarditis in patients with congenital heart disease (CHD), particularly those with previously operated cyanotic or conotruncal anomalies (24–27), as further detailed in the Online Appendix. These findings bring important perspective to the issue of endocarditis after TPVR, which is typically performed in patients with demographic and medical features that place them at higher risk than anyone for this outcome.

CHALLENGES IN THE DIAGNOSIS AND MANAGEMENT OF ENDOCARDITIS AFTER TPVR. In prior reports, criteria for defining endocarditis and for study inclusion varied, as did the clinical spectrum of affected patients. While most or all patients with endocarditis in some series had clear TPV involvement and/or a severe clinical presentation, other studies were notable for few endocarditis cases with valve involvement or severe presentation. These differences may reflect random variation, center differences, or inconsistent thresholds for diagnosing endocarditis in this population, and they highlight the uncertainty around this issue. In the current study, investigator-reported adverse event codes were used for analysis. However, we observed that 8 of 34 patients coded as TPV-related endocarditis during the first episode had no documented evidence of TPV involvement, reflecting

FIGURE 1 Competing Outcomes



The competing outcomes curve depicts cumulative incidences over time of endocarditis **(blue line)**, explant without endocarditis **(orange line)**, and death without explant or endocarditis **(gray line)**, whereas the probability of being alive without any events is represented by the **red line**. TPVR = transcatheter pulmonary valve replacement.

the investigators' assessment that the infection was related to the device despite no documentation of TPV vegetations or dysfunction.

The inadequacy of current systems for defining endocarditis of the RVOT in patients with repaired CHD confounds efforts to understand the spectrum and outcomes of endocarditis in this population, and to advance their management (12). This is illustrated in the current series by the discordance between investigator-assigned endocarditis type (TPV-related or not related) and objective evidence of valve involvement in some cases, which is likely to be one of the main drivers of decision-making about whether to intervene surgically or with another transcatheter procedure. Accordingly, a modified system for diagnosing post-TPVR endocarditis may be helpful, but there are insufficient data from pathologically documented cases to propose a rigorous classification based on direct confirmation along the lines of the modified Duke criteria. Thus, we proposed a new alphanumeric clinical categorization, which appears useful for assessing the clinical severity and major

TABLE 5 Endocarditis Incidence Rates and Rate Ratios According to Center Volume (Implants During the Trial) and Specific Trial

		Any Endocarditis					TPV-Related Endocarditis				
Group	No. of Implants	Patient-Years Follow-Up	No. of Cases*	IR (95% CI)	IR Ratio (95% CI)	p Value	Patient-Years Follow-Up	# Cases*	IR (95% CI)	IR Ratio (95% CI)	p Value
No. of implants											
Centers with ≤15	117	489.4	21	4.3 (2.8–6.6)	1.6 (0.9–2.8)	0.088	489.4	19	3.9 (2.5–6.1)	2.3 (1.2–4.3)	0.010
Centers with >15	192	1,170.9	31	2.7 (1.9–3.8)			1,170.9	20	1.7 (1.1–2.7)		
Trial											
IDE	148	968.6	27	2.8 (1.9–4.1)	1.3 (0.6–3.3)	0.51	968.6	17	1.8 (1.1–2.8)	1.0 (0.4–2.8)	0.98
PAS	99	402.6	19	4.7 (3.0–7.4)	2.3 (0.9–5.7)	0.08	402.6	17	4.2 (2.6–6.8)	2.4 (0.9–6.6)	0.08
PMSS	62	289.1	6	2.1 (0.9–4.6)	Ref		289.1	5	1.7 (0.7–4.2)		

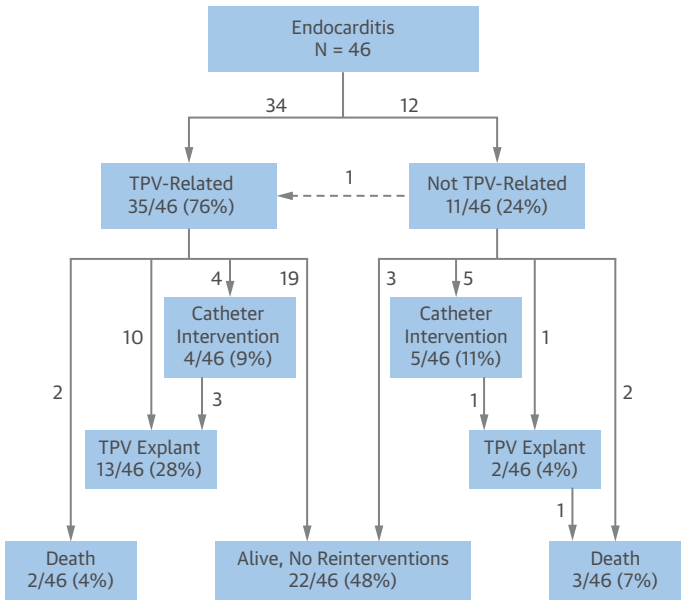
Incidence rates (IR) with 95% confidence intervals (CIs) are for each group, and IR ratios are within each category relative to the reference (Ref) group. The p values are from Wald chi-squared test.
*Number of cases of endocarditis (any or TPV-related).

IDE = Post-Approval Study of the original U.S. Investigational Device Exemption; PAS = U.S. Post-Approval Study; PMSS = Post-Market Surveillance Study.

outcomes of endocarditis after TPVR, and potentially for RVOT/pulmonary valve endocarditis more broadly. Although additional data will be necessary to confirm the utility of this clinical scheme, it may help facilitate both appropriate and timely treatment as well as epidemiological observation and analysis that will lead to more effective prevention, identification, and treatment. While this system was not applied prospectively, we recommend its application in future reports, which will hopefully allow some standardization across the published data and facilitate deeper insights into the risk of and risk factors for endocarditis in this population.

In addition to unclear diagnostic criteria, there are several important but unresolved considerations in the management of patients who present with possible endocarditis, as well as evolution in practice around documenting TPV involvement, notably the use of intracardiac echocardiography. These and other factors are discussed further in the Online Appendix (28-32). One of the most consequential scenarios is the patient with severe or rapidly progressive RVOT and/or RV dysfunction, which may be the only indication of the obstruction. As we propose in Online Figure 1, these patients may benefit from temporary stabilization with extracorporeal membrane oxygenation then transcatheter relief of RVOT obstruction, either with a stent or a second TPV, followed later by surgical pulmonary valve replacement.

FIGURE 2 Management and Outcomes of Endocarditis



This flow diagram depicts outcomes after the first endocarditis diagnosis according to investigator-designated TPV involvement. One of the 12 patients initially diagnosed with non–TPV-related endocarditis was subsequently diagnosed with a second infection that was considered TPV-related, such that the total number of TPV-related cases increased from 34 to 35. That patient had no intervention (other than medical) with the first episode, and TPV explant after the second. "Alive, No Reinterventions" refers to the outcome status related to the endocarditis episode. This diagram does not account for late reinterventions or explants unrelated to the endocarditis episode. Of the 6 patients coded as "non–TPV-related who required interventions, 2 had vegetations, 1 had significant RVOT obstruction, and 3 had pre-existing RVOT obstruction. Two other patients with non–TPV-related endocarditis died later, unrelated to the endocarditis episode: the first patient, who received a second valve after a full course of antibiotic therapy and sterilization of cultures, died 4 months later from hemorrhagic shock due to bleeding from a bronchial arterial malformation; the second patient, whose endocarditis was treated medically (i.e., no interventions) and was reported as resolved, died of unknown cause and circumstances 11 months after the endocarditis diagnosis. TPV = transcatheter pulmonary valve.

CONSIDERATIONS OF PVR METHOD, VALVE TYPE, AND THE LARGER CONTEXT. An important question is whether the risk of endocarditis is different after TPVR with a Melody valve than after surgical PVR or conduit replacement or after TPVR with other types of valves. These questions cannot be answered definitively at this point, in part due to lack of information parity. In this study, patients were followed prospectively after TPVR for an unprecedented 1,660 patient-years. Studies on endocarditis after RVOT surgery are usually retrospective, with data of variable quality, and are generally limited to cases of endocarditis that lead to reoperation. As concern about post-TPVR endocarditis has emerged, there have been more investigations of endocarditis after RVOT surgery (7,8,11,32,33). Several studies reported a higher rate of endocarditis after TPVR than surgical conduit replacement, and implied a bacterial predilection for bovine jugular vein tissue (7,8), but a recent laboratory investigation cast doubt on this hypothesis (34). More recently, Lluri et al. (11) reported no difference in endocarditis rates between TPVR and contemporaneous surgical PVR patients, despite the fact that conduits and prior endocarditis were more prevalent in TPVR patients. While heightened attention to this issue is encouraging, data regarding endocarditis after surgical RVOT procedures remain inadequate, and important gaps remain. For example, in a recent review of the Society of Thoracic Surgeons database, it was reported that 12% of adults undergoing PVR had a prior history of endocarditis, which is higher than surgical reports would suggest (35). Clearly, there is a need for more robust data on endocarditis in patients with complex right-sided CHD, particularly after RVOT intervention.

There are few published studies of outcomes after TPVR with other types of valves, and those included short follow-up and small numbers of patients. The

most extensive source of data on outcomes after TPVR with Sapien valves, and the best available comparator for endocarditis after Melody valve implant, can be found in the instructions for use for the Sapien XT in the pulmonary position, which reported 219.8 patient-years of follow-up on 79 catheterized patients, 69 of whom received a TPV (21). In the 79-patient safety cohort, the estimated freedom from endocarditis was 86.1% at 5 years; the risk of endocarditis would presumably be higher if based only on the 69 implanted patients. Simple comparison of those data with the findings of the current study (89% freedom from any endocarditis at 5 years) suggests minimal or no difference.

Hascoet et al. (10) recently reported their single-center experience with TPVR in 79 patients over 9 years and concluded that endocarditis risk was higher in patients who received a Melody valve than those in whom a Sapien was implanted. However, their analysis was beset by several important biases and limitations that are worth noting. They described an atypically high rate of endocarditis in patients that was inconsistent with the larger published data on this topic, and most cases were very early in their experience, which may suggest a center-specific phenomenon or a learning curve effect. Of the 8 patients who developed endocarditis in their experience, 7 were implanted before April 2010, after which they modified their periprocedural antibiotic and anticoagulation therapy. Their first Sapien implant occurred after this change, in December 2011. There were other important issues related to study design and execution as well. Specifically, Melody and Sapien cohorts were not contemporaneous, and there was a large discrepancy in the median duration of follow-up between the Melody (4.9 years) and Sapien (1.0 years) cohorts, which is critical in evaluation of this time-dependent outcome, given that most cases of post-TPVR endocarditis occur more than 1 year after implant (12). Furthermore, the features of the cohorts differed in several important respects. For example, one-half of Sapien implants were into a native or patched RVOT or a bioprosthetic valve, compared with only 12% of Melody implants, and, as they observed and others reported, endocarditis is uncommon after TPVR into a native/patched RVOT (5,11,12). Moreover, risk factors for endocarditis, including RVOT stenosis, smaller diameter valves, and younger age, were more common in the Melody cohort, while data were not provided for potentially important mitigating factors such as post-TPVR RVOT gradient. Considering the statistically small cohort and the aforementioned limitations and confounding factors, their conclusions were not robustly supported by the data presented.

At present, there is no compelling evidence to support the claim that endocarditis incidence rates and outcomes differ between TPVR and surgical PVR or between TPV valve types. Regardless, it is important to consider the overarching risk-benefit profile for all options and not let the perceived risk of endocarditis alone drive decisions about therapy. It is possible, for example, that the risk of endocarditis may differ between therapies but that the aggregate profile may still favor an option that is associated with higher endocarditis risk. In other words, endocarditis risk should not be the only driver of which mode or type of valve replacement is pursued. Moving forward, it is essential that the community continues to track and report endocarditis after both TPVR and surgical conduit/valve replacement with all types of devices. Utilizing a standardized classification system such as the scheme proposed in this study may facilitate comparison and analysis of this important outcome.

PREVENTION. While this study did not assess the relationship between preventive or behavioral factors and endocarditis, it is worth reinforcing practices that are based on observed or hypothetical risk factors for endocarditis in hopes of reducing the incidence rate of this complication. Prior to catheterization, it is appropriate to ascertain factors such as a history of endocarditis and medical or behavioral risk factors for bacteremia, and to evaluate and treat potential patient-related risk factors, including problematic dentition and skin or mucosal breakdown. Following TPVR, education of the patient, family, and primary physicians regarding signs and symptoms of endocarditis, as well as the importance of prompt and thorough evaluation of fever, is critical. Younger patients were at higher risk of endocarditis in this series, which supports particular diligence in educating pediatric/adolescent patients and their families about the importance of preventive measures. For patients with any prosthetic RVOT conduit or valve, physicians should maintain a high index of suspicion for endocarditis. Data from animal studies suggest that antiplatelet or anticoagulant therapy may reduce endocarditis risk, consistent with the pathogenesis of endocarditis, which merits investigation in the TPVR population (36-38).

STUDY LIMITATIONS. The limitations of this study were similar to those acknowledged previously (4). Endocarditis cases were diagnosed and managed at the discretion of clinicians at each site, with no

central adjudication or standard practice for prospectively assessing TPV involvement. Pathology data for explanted TPV devices were not available in most cases, limiting our ability to confirm the diagnosis of endocarditis or definitively evaluate TPV involvement. Accordingly, findings may have been affected by ascertainment or classification bias or practice variation. To offset potential bias, we included all patients reported to have endocarditis, adopted an inclusive definition of TPV-related endocarditis, and re-evaluated infectious adverse events other than endocarditis to determine if they should have been reclassified. Also, background data that may have permitted insight into risk factors for post-TVPR endocarditis (e.g., prior endocarditis history, other potential risk factors) were not ascertained prospectively. Competing risk methods were not used to assess covariates associated with time-dependent outcomes.

CONCLUSIONS

Endocarditis is an important adverse outcome after TVPR and in children and adults with post-operative CHD involving the RVOT. Clinicians should maintain a high level of concern about endocarditis with Staphylococcus aureus, which was most often associated with severe clinical presentation and mortality. A clinical classification system proposed in this report may help standardize approaches to this complication of TPVR and facilitate efforts to analyze and pool data across studies. It will be important to determine risk factors not only for endocarditis generally, but in particular for endocarditis manifesting with severe RVOT obstruction and clinical instability. Ultimately, ongoing efforts to understand, prevent, and optimize management of this complication will be paramount in making the best use of TPV therapy. Given the prevalence of mitigating and predisposing conditions and the high risk of endocarditis in this population overall, efforts to educate patients and caregivers about risk and about best practices for risk reduction are essential to reducing endocarditis rates after TPVR.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: A risk of endocarditis persists 5 years after transcatheter deployment of the Melody valve prosthesis in the pulmonary position.

TRANSLATIONAL OUTLOOK: Better systems for assessing the severity and clinical outcomes of endocarditis are needed for use in patients with repaired right-sided congenital heart defects, including those who have received prosthetic pulmonary valves or conduits.

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KEY WORDS infection, percutaneous valve, pulmonary valve, tetralogy of Fallot

APPENDIX For expanded Methods, Results, and Discussion sections as well as a supplemental figure, please see the online version of this paper.