JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 75, NO. 4, 2020

PUBLISHED BY ELSEVIER

Adverse Events, Radiation Exposure, and Reinterventions Following Transcatheter Pulmonary Valve Replacement

Bryan H. Goldstein, MD,[a] Lisa Bergersen, MD, MPH,[b] Aimee K. Armstrong, MD,[c] Brian A. Boe, MD,[c] Howaida El-Said, MD,[d] Diego Porras, MD,[b] Shabana Shahanavaz, MD,[e] Ryan A. Leahy, MD,[f] Jacqueline Kreutzer, MD,[a] Jeffrey D. Zampi, MD,[g] Michael R. Hainstock, MD,[h] Todd M. Gudausky, MD,[i] George T. Nicholson, MD,[j] Kimberlee Gauvreau, ScD,[b] Andrea Goodman, MPH,[b] Christopher J. Petit, MD[k]

ABSTRACT

BACKGROUND Transcatheter pulmonary valve replacement (TPVR) is associated with a risk of procedural serious adverse events (SAE) and exposure to ionizing radiation.

OBJECTIVES The purpose of this study was to define the risk of, and associations with, SAE and high-dose radiation exposure using large-scale registry data.

METHODS The analysis of the multicenter C3PO-QI registry was limited to patients who underwent TPVR from January 1, 2014, to December 31, 2016. SAE were defined as the occurrence of ≥1 moderate, major, or catastrophic events. Radiation dose was reported as dose area product adjusted for weight. Associations with outcome measures were explored in univariate and multivariable analyses.

RESULTS A total of 530 patients (59% male) underwent TPVR at a median age of 18.3 years (interquartile range [IQR]: 12.9 to 27.3 years) and weight of 58 kg (IQR: 43 to 77 kg) at 14 centers. Implant substrate included homograft (41%), bioprosthesis (30%), native right ventricular outflow tract (RVOT) (27%) and other (2%). TPVR indications were pulmonary insufficiency (28%), stenosis (23%), and mixed (49%). AE and SAE occurred in 26% and 13% of cases, respectively, including 1 mortality. SAE were more frequent in homograft conduit than other RVOT substrates, although SAE type and severity differed between implant substrates. Median radiation dose was 198 $\mu Gy \cdot m^2/kg$ (IQR: 94 to 350 $\mu Gy \cdot m^2/kg$). Higher radiation dose was associated with older age, greater RVOT obstruction, and concomitant interventions ($p < 0.001$). During a median follow-up duration of 1 year, 13.3% underwent catheterization, surgery, or both, unrelated to infection. Younger age, smaller size, and hemodynamic and anatomic factors indicative of greater RVOT obstruction were associated with TPV reintervention.

CONCLUSIONS The incidence of SAE during TPVR in the C3PO-QI registry is high, but mortality is uncommon. Radiation dose is greater than for other congenital interventions and is associated with patient and procedural factors. Reintervention is common during early follow-up. (J Am Coll Cardiol 2020;75:363–76)

Listen to this manuscript's audio summary by Editor-in-Chief Dr. Valentin Fuster on JACC.org.

From the [a]Heart Institute, UPMC Children's Hospital of Pittsburgh and Department of Pediatrics, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; [b]Department of Cardiology, Boston Children's Hospital, Boston, Massachusetts; [c]The Heart Center, Nationwide Children's Hospital, Columbus, Ohio; [d]Division of Cardiology, Rady Children's Hospital, San Diego, California; [e]Division of Pediatric Cardiology, St. Louis Children's Hospital, St. Louis, Missouri; [f]Department of Cardiology, Norton Children's Hospital, Louisville, Kentucky; [g]Divison of Pediatric Cardiology, University of Michigan Medical School, Ann Arbor, Michigan; [h]Division of Pediatric Cardiology, University of Virginia Children's Hospital, University of Virginia, Charlottesville, Virginia; [i]Division of Cardiology, Children's Hospital of Wisconsin, Milwaukee, Wisconsin; [j]Division of Pediatric Cardiology, Monroe Carell Jr. Children's Hospital at Vanderbilt University Medical Center, Nashville, Tennessee; and the [k]Division of Pediatric Cardiology, Children's Healthcare of Atlanta Sibley Heart Center, Emory University School of Medicine, Atlanta, Georgia. The C3PO-QI registry is funded, in part, by a grant from the Children's Heart Foundation. Dr. Goldstein has served as a consultant for Medtronic, Edwards Lifesciences, and W.L. Gore & Associates. Dr. Armstrong has served as a consultant for and received research grants from Medtronic and Edwards Lifesciences; and has received research support from Edwards Lifesciences.

ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2019.11.042

ABBREVIATIONS AND ACRONYMS

CHD = congenital heart disease

DAP = dose area product

PA = pulmonary artery

PI = pulmonary insufficiency

PS = pulmonary stenosis

RV = right ventricle/ventricular

RVOT = right ventricular outflow tract

SAE = serious adverse event

TPVR = transcatheter pulmonary valve replacement

Since the original description of transcatheter pulmonary valve replacement (TPVR) by Bonhoeffer et al. (1) in 2000, the use of TPVR for treatment of dysfunctional right ventricular outflow tract (RVOT) conduits has grown rapidly (2). TPVR therapy is now employed in multiple non-RVOT conduit pulmonic substrates, including the dysfunctional bioprosthetic pulmonary valve (3), left ventricular outflow tract conduit (4), and patch-augmented RVOT (5,6). Despite the increasing frequency of TPVR procedures, our knowledge of their safety and efficacy is derived almost exclusively from manufacturer-sponsored clinical trial data. While rigorous trial data do provide excellent insight into procedural safety and outcomes, the strictly developed trial cohorts may limit generalizability, especially in the era of widespread clinical adoption across heterogenous patients and implantation substrates.

SEE PAGE 377

At present, there are limited descriptors of clinical hazards during and after TPVR, with much of the existing published data focused on serious adverse events (SAE). Evidence suggests that TPVR is associated with a high rate of SAE, ranging from 6% to 13.3% in published trial data (4,7–10). The incidence of SAE has not been confirmed in a "real-world" cohort of clinical patients undergoing TPVR, although there is reason to suspect the SAE rate outside of a trial may be higher, given the lack of strict inclusion and exclusion criteria and more variable procedural methodology. Meanwhile, emerging data suggest that TPVR has one of the highest radiation dose exposures of interventional procedures performed in the congenital catheterization laboratory (11,12). In the setting of mounting evidence of the increased lifetime cancer risk in congenital heart disease (CHD) patients from serial exposure to ionizing radiation, this hazard is salient (13–15). Most TPVR recipients will undergo subsequent interventional procedures with further accumulation of lifetime radiation exposure. Thus, it is imperative to identify modifiable factors associated with high radiation dose to facilitate efforts at achieving dose reduction. Last, TPVR therapy is but 1 component in the lifetime management of the CHD patient with RVOT dysfunction. To the extent that TPVR is not "curative," better understanding the clinical outcomes of patients post-TPVR potentially offers insight into both the durability of the treatment and the complexity of the treated population.

The C3PO-QI (Congenital Catheterization Collaborative Project on Outcomes-Quality Improvement) registry is a long-standing multicenter initiative to develop performance and quality metrics for patients with CHD undergoing cardiac catheterization. Given limited evidence related to TPVR procedures available outside of clinical trials, we sought to utilize the C3PO-QI registry to define the risk of, and associations with, SAE and high-dose radiation exposure. We further sought to describe clinical outcomes following TPVR.

METHODS

Data for this study were obtained from the C3PO-QI registry, which contains prospective collected entries using a web-based data collection tool at 17 participating institutions that have agreed to enrollment, 14 of which were included in this analysis. The 3 sites with incomplete data collection for the study period were excluded. Specific details of this registry have been published previously (16). A follow-up data collection component was embedded within the C3PO-QI TPV module to facilitate collection of clinical outcomes data following hospital discharge from TPVR. Data were included from the C3PO-QI registry for the study period of January 1, 2014, through December 31, 2016. Institutional review board approval (or equivalent) was obtained at all participating centers. In accordance with participant agreements, all interventional cardiologists who contributed to the dataset reviewed and approved the manuscript prior to peer review submission.

POPULATION. This study analyzed C3PO-QI data collected surrounding cardiac catheterizations for TPVR. All patients who underwent TPVR and had the TPV module completed within the C3PO-QI registry were eligible for inclusion. Exclusion criteria included placement of the TPV in a nonpulmonary position or a nonpercutaneous approach to TPVR

Dr. Shahanavaz has served as a consultant for Medtronic and Edwards Lifesciences. Dr. Kreutzer has served as a consultant for Medtronic and Edwards Lifesciences; and has received research grant support from Siemens. Dr. Gudausky has served as a consultant for Medtronic, Inc. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received August 22, 2019; revised manuscript received September 26, 2019, accepted November 11, 2019.

(e.g., hybrid delivery from a transthoracic approach). Patients with aortopulmonary transposition and a subpulmonic left ventricle (4) were included in the cohort. Patient and procedural characteristics were available for each encounter. Diagnosis was defined as the patient's primary cardiac diagnosis as assigned by the treating physician. RVOT substrate was grouped into 4 types: bioprosthesis, homograft, native (including patch augmented), and other. Procedural indication was defined by the treating physician as pulmonary stenosis (PS), pulmonary insufficiency (PI), or mixed pulmonary stenosis and insufficiency (PS/PI). Procedural data including anatomic findings, hemodynamic measures, and interventions were collected. Calcification score was defined previously and graded between none and severe (17). TPV implants included Melody TPV (20- and 22-mm Melody TPV, Medtronic, Dublin, Ireland) and Edwards Sapien THV (Sapien THV, Sapien XT, and Sapien 3, Edwards Lifesciences, Irvine, California).

ADVERSE EVENTS. Adverse events (AE) were defined in the C3PO-QI registry as any anticipated or unanticipated event for which avoidable injury occurred, or could have occurred, as a potential or definite consequence of performance of the catheterization (18). AEs were recorded at the time of identification either during the procedure or following the procedure. Information recorded included event name, a brief description, and attribution. All AEs underwent independent review by 2 interventional cardiologists for consistent severity classification using established standardized nomenclature on a 5-level severity scale, based on clinical impact (1: none, 2: minor, 3: moderate, 4: major, 5: catastrophic/death) (18,19). SAEs were defined as level 3, 4, or 5 events. If multiple AEs occurred during a single procedure, the highest-grade AE recorded was utilized in this analysis.

RADIATION METRICS. Radiation dose metrics were recorded as fluoroscopy time (minutes), air kerma (mGy), and dose area product (DAP) ($\mu Gy \cdot m^2$). DAP was also indexed to body weight and reported as $\mu Gy \cdot m^2/kg$ or DAP/kg. The use of stored fluoroscopy was defined by the use of at least 1 stored digital fluoroscopy during the procedure. Use of 3-dimensional rotational angiography was defined by the acquisition of at least 1 rotational angiogram with 3-dimensional reconstruction during the procedure.

CLINICAL FOLLOW-UP. A limited follow-up component was embedded within the TPV data collection module, and included data fields for: vital status, post-TPVR catheterization (diagnostic and interventional), reintervention (surgical and transcatheter), bloodstream infection (BSI), and infective endocarditis (IE). For purposes of this analysis, post-TPVR reintervention included any cardiac catheterization (diagnostic, interventional, electrophysiologic) and cardiac surgery. Sites were asked to complete this follow-up module for each TPV recipient at the time of data collection for this study.

TABLE 1 Baseline Characteristics

	Total (N = 530)	Melody (n = 465)	Sapien (n = 65)
Male	314 (59)	277 (60)	37 (57)
Age, yrs	18.3 (12.9, 27.3)	17.9 (12.7, 26.7)	19.3 (16.4, 33.3)
Weight, kg	58 (43, 77)	58 (42, 77)	62 (52, 79)
Cardiac diagnosis			
Tetralogy of Fallot	276 (52)	232 (50)	44 (68)
Aortic valve disease	41 (8)	36 (8)	5 (8)
Truncus arteriosus	33 (6)	32 (7)	1 (2)
Pulmonary valve disease	24 (5)	17 (4)	7 (11)
PA/IVS	15 (3)	14 (3)	1 (2)
Double outlet right ventricle	17 (3)	15 (3)	2 (3)
TGA/CCTGA	21 (4)	21 (5)	0 (0)
Other	47 (9)	43 (9)	4 (6)
Not recorded	56 (11)	55 (12)	1 (2)
Noncardiac diagnosis	58 (11)	45 (10)	13 (20)
Genetic syndrome	49 (9)	46 (10)	3 (5)
Prior endocarditis	22 (4)	20 (4)	2 (3)
RVOT type			
Bioprosthesis	161 (30)	149 (32)	12 (18)
Homograft conduit	218 (41)	202 (43)	16 (25)
Native/patch-augmented	143 (27)	107 (23)	36 (55)
Other	8 (2)	7 (2)	1 (2)
Nominal conduit diameter	22 (19, 24)	21 (19, 24)	25 (22, 27)
Existing TPV implant	32 (6)	24 (5)	8 (12)
Existing RVOT stent	51 (10)	41 (9)	10 (15)
Procedural indication			
PS	123 (23)	117 (25)	6 (9)
Pulmonary insufficiency (PI)	150 (28)	112 (24)	38 (58)
Mixed PS/PI	257 (49)	236 (51)	21 (32)

Values are n (%) or median (25th, 75th percentile).

CCTGA = congenitally corrected transposition of the great arteries; PA/IVS = pulmonary atresia with intact ventricular septum; PI = pulmonary insufficiency; PS = pulmonary stenosis; RVOT = right ventricular outflow tract; TGA = transposition of the great arteries; TPV = transcatheter pulmonary valve.

STATISTICAL ANALYSIS. Categorical variables are summarized with frequencies and percentages, and continuous variables with medians and interquartile ranges (IQR) (25th, 75th percentile). Patient and procedural characteristics were compared for patients who experienced a SAE and those who did not using Fisher exact test for categorical variables, and the Wilcoxon rank sum test for continuous variables. Associations between DAP and patient characteristics were evaluated using the Wilcoxon rank sum test and Spearman correlation coefficients. Forward stepwise selection was used for multivariable linear regression

TABLE 2 Procedural Characteristics

	Baseline/Procedural	Post-TPVR
Procedure time, min	168 (129, 217)	
Calcification score		
None/trivial	252 (48)	
Mild	104 (20)	
Moderate	85 (16)	
Severe	69 (13)	
Not reported	20 (4)	
RVSP, mm Hg	59 (44, 74)	40 (33, 48)
RV-PA gradient, mm Hg	31 (15, 43)	9 (5, 15)
PI grade		
None/trivial	54 (10)	487 (92)
Mild	68 (13)	24 (5)
Moderate	155 (29)	3 (1)
Severe	240 (45)	1 (0.1)
Not recorded	13 (2)	15 (3)
Baseline RVOT minimal diameter, mm	15 (11, 19)	
Coronary assessment performed	428 (81)	
Number of pre-stents placed		
0	163 (31)	
1	169 (32)	
2	138 (26)	
≥3	60 (11)	
Concomitant non-RVOT interventions	96 (18)	
TPV implant diameter	22 (20, 22)	
Ratio of baseline RVOT diameter to implant diameter	0.72 (0.55, 0.87)	
Post-TPV implant re-dilation	104 (20)	

Values are median (25th, 75th percentile) or n (%).

AE = adverse event; RV-PA = right ventricle to pulmonary artery; RVSP = right ventricular systolic pressure; other abbreviations as in Table 1.

analysis; variables significant at the 0.20 level in univariate analysis were considered for inclusion, and $p < 0.05$ by the likelihood ratio test was required for inclusion in the final model. Because DAP is not normally distributed, a natural log transformation was used. Statistical significance was assessed at the 0.05 level.

RESULTS

PATIENTS AND PROCEDURES. During the 3-year period from 2014 to 2016, data were collected on 530 TPVR procedures performed at 14 institutions. As demonstrated in Table 1, median age was 18.3 years (IQR: 12.9 to 27.3 years) and weight was 58 kg (IQR: 43 to 77 kg). Tetralogy of Fallot was the most common underlying cardiac diagnosis (52%). Table 1 also depicts the breakdown in patient characteristics when stratified by type of TPV implant, including Melody (87.7%) and Sapien (12.3%) valves.

Procedural characteristics are detailed in Table 2. Following TPVR, right ventricular (RV) to pulmonary artery (PA) gradient fell from a baseline of 31 mm Hg (IQR: 15 to 43 mm Hg) to 9 (IQR: 5 to 15 mm Hg). The PI grade improved from moderate or severe in 74% of cases at baseline to trivial/none (94.5%) or mild (4.7%) in all but 4 cases. Pre-implantation coronary artery assessment was performed in the majority of patients, but was not performed in 19% of cases, which included implants in the native (35%), homograft (35%) and bioprosthetic (30%) RVOT substrates. At least 1 pre-TPV stent was placed in 69% of cases. Concomitant non-RVOT interventions were performed in 18% of procedures.

ADVERSE EVENTS. The overall reported AE rate in this population was 26.2% (Table 3). SAE occurred 79 times in 13% of procedures. While there were no differences in the rate of AE when stratified by implant substrate (homograft, bioprosthesis, or native RVOT), SAE were more common in homograft conduits ($p = 0.022$). The most common SAE were related to vascular/conduit injury (5.8% of all cases), tachyarrhythmia or bradyarrhythmia (1.7%), and non-TPV stent problems (1.7%). There were no events related to coronary artery injury or compression. Three patients required procedural extracorporeal membrane oxygenator (ECMO) support (0.6%), but 2 of these patients had ECMO in place prior to attempted rescue TPVR. There were 4 (0.8%) periprocedural deaths, only 1 of which was deemed to be the result of an SAE. In 6 cases (1.1%) where the intention was to place a single TPV in the RVOT, >1 TPV was implanted. This was most common in the native RVOT cohort (2.1%).

TPV malposition or embolization, requiring additional therapy, occurred in 5 cases (0.9%). In 2 of these cases, the TPV was able to be secured with implantation of additional stents or a second TPV. The TPV remained unstable in 1 case, prompting surgical TPV removal and pulmonary valve replacement. In the fourth case, despite implantation of a second TPV for treatment of initial TPV malposition, the TPV complex embolized to the right ventricle, inverted, and became lodged in the RVOT, resulting in a loss of cardiac output necessitating ECMO initiation with eventual mortality. Two additional mortalities encountered in this cohort both occurred in nonoperative candidates referred for rescue TPVR, who were on ECMO prior to the procedure, but no AEs were identified in these patients. The final mortality occurred in an adult patient following successful and uncomplicated TPV implantation, performed as an inpatient. Following transfer back to the referring institution, the patient required increased respiratory support until she expired on post-catheterization

TABLE 3 Adverse Events

	Total (N = 530)	RVOT Implant Substrate			p Value
		Homograft* (n = 226)	Bioprosthesis (n = 161)	Native (n = 143)	
Any AE	139 (26)	69 (31)	33 (21)	37 (26)	0.087
Grade of most serious AE					0.19
Level 1 (none)	1 (1)	0 (0)	1 (3)	0 (0)	
Level 2 (minor)	69 (50)	29 (42)	18 (55)	22 (59)	
Level 3 (moderate)	63 (45)	38 (55)	13 (39)	12 (32)	
Level 4 (major)	5 (4)	2 (3)	1 (3)	2 (5)	
Level 5 (catastrophic)	1 (1)	0 (0)	0 (0)	1 (3)	
Any SAE†	69 (13)	40 (18)	14 (9)	15 (10)	0.022
Access-related					
Moderate	4 (0.8)	1 (0.4)	1 (0.6)	2 (1.4)	
Arrhythmia					
Atrial	4 (0.8)	4 (1.8)	0 (0)	0 (0)	
Ventricular	3 (0.6)	1 (0.4)	1 (0.6)	1 (0.7)	
Heart block (3rd degree)	2 (0.4)	1 (0.4)	1 (0.6)	0 (0)	
Stent related					
Stent malposition or embolization	8 (1.6)	3 (1.3)	1 (0.6)	4 (2.8)	
Stent fragment embolization	1 (0.2)	0 (0)	1 (0.6)	0 (0)	
TPV-related					
TPV malposition/embolization	5 (0.9)	2 (0.9)	1 (0.6)	2 (1.4)	
Balloon rupture during TPV implant with TPV dysfunction requiring 2nd TPV	1 (0.2)	1 (0.4)	0 (0)	0 (0)	
TPV implant balloon failure to deflate, requiring CPR	1 (0.2)	0 (0)	0 (0)	1 (0.7)	
TPV removed after unsheathing	1 (0.2)	1 (0.4)	0 (0)	0 (0)	
Acute diagnosis of endocarditis	1 (0.2)	1 (0.4)	0 (0)	0 (0)	
Unanticipated implantation of >1 TPV device	6‡ (1.1)	3 (1.3)	0 (0)	3 (2.1)	
Equipment-related					
Balloon rupture with fragment embolization requiring retrieval	2 (0.4)	1 (0.4)	1 (0.6)	0 (0)	
Pacing catheter complication	1 (0.2)	0 (0)	0 (0)	1 (0.7)	
Vascular injury (not access-related)					
Conduit injury (contained)	23 (4.3)	20 (8.8)	3 (1.9)	0 (0)	
PA vascular injury (including pseudoaneurysm)	4 (0.8)	3 (1.3)	1 (0.6)	0 (0)	
PA guidewire injury	4 (0.8)	1 (0.4)	2 (1.2)	1 (0.7)	
Cardiac injury					
Tricuspid valve injury	2 (0.4)	0 (0)	0 (0)	2 (1.4)	
Airway/hemodynamic					
Pulmonary edema or hemorrhage	5 (0.9)	2 (0.9)	2 (1.2)	1 (0.7)	
Hypotension requiring medication	1 (0.2)	1 (0.4)	0 (0)	0 (0)	
Post-TPV respiratory insufficiency	2 (0.4)	2 (0.9)	0 (0)	0 (0)	
Other					
Neurological injury (cerebrovascular accident)	1 (0.2)	0 (0)	0 (0)	1 (0.7)	
Thrombosis	1 (0.2)	0 (0)	1 (0.6)	0 (0)	
Medication reaction	1 (0.2)	1 (0.4)	0 (0)	0 (0)	
Urinary catheter injury	1 (0.2)	0 (0)	0 (0)	1 (0.7)	
ECMO					
In place at procedure start	2 (0.3)‡				
Initiated emergently during procedure	1 (0.1)				
Mortality	4 (0.8)‡				

Values are n (% of procedures with this event). *Homograft also includes other conduit types (nonvalved tube). †Characteristics of all reported SAE (79 SAE in n = 69). ‡Not included as independent adverse events. Only 1 mortality was deemed to be related to the TPV implant procedure; this occurred in a patient with native RVOT substrate.

CPR = cardiopulmonary resuscitation; ECMO = extracorporeal membrane oxygenator; PA = pulmonary artery; TPV = transcatheter pulmonary valve.

TABLE 4 Radiation Metrics

Laboratory type	
Single plane	4 (1)
Biplane	526 (99)
Fluoroscopy time, min	42 (28, 59)
Air Kerma, mGy	
Total	948 (411, 1,934)
Frontal	360 (165, 786)
Lateral	516 (200, 1,138)
DAP, μGy·m^2	
Total	10,169 (4,765, 21,675)
Frontal	4,111 (1,813, 9,258)
Lateral	5,018 (1,830, 11,240)
Total Indexed DAP, DAP/kg; μGy·m^2/kg	198 (94, 350)
Rotational angiography with 3D reconstruction	56 (11)

Values are n (%) or median (25th, 75th percentile).
3D = 3-dimensional; DAP = dose area product.

day 3. Two balloon malfunctions occurred with clinical sequelae. In 1 case, following a difficult advancement of the delivery system to the RVOT but successful deployment of a Sapien valve, the balloon would not deflate. This rapidly led to hypotension followed by the onset of ventricular tachycardia. Cardiopulmonary resuscitation was initiated, and the inflated balloon was withdrawn into the inferior vena cava, where it slowly deflated. In a separate case, rupture of the delivery balloon occurred during Melody TPV implantation, which resulted in substantial PI post-TPVR, presumably due to TPV leaflet injury. A second TPV implant was placed.

Conduit injury occurred in 4.3% of all cases and 8.8% of cases involving a homograft conduit. Given the high incidence, and frequent clinical irrelevance, of hemodynamically insignificant contained conduit injury during TPVR procedures, we performed an additional analysis following exclusion of these cases. As demonstrated in Online Table 1, the overall AE and SAE rates were modestly lower, at 23% and 9%, respectively, after exclusion of contained conduit injuries.

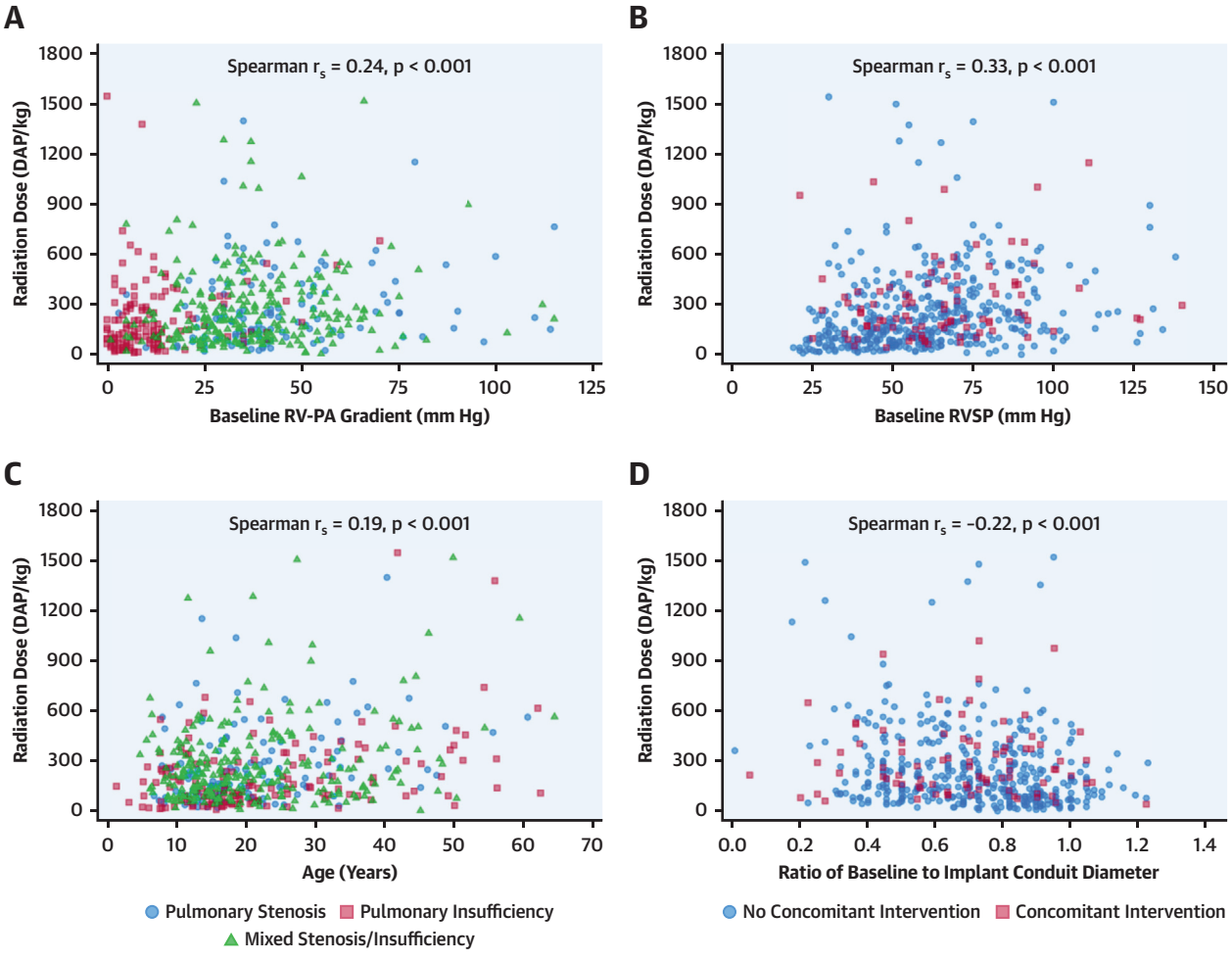
RADIATION DOSE. TPVR procedures were almost universally performed in biplane catheterization laboratories (99.2%). Radiation metrics are displayed in **Table 4**. Univariate factors associated with radiation dose, as expressed in DAP/kg, are explored in Online Table 2 and **Figure 1**. RVOT substrate and procedural indication consistent with PS, along with older age and greater weight, were each correlated with higher dose. Patient and procedural factors reflecting the complexity and degree of RVOT stenosis, presence of non-RVOT concomitant interventions, as well as AE, were also related to dose. Factors that remained significantly associated with higher radiation dose on multivariable analysis (**Table 5**) included older age, higher baseline RV systolic pressure, use of ≥2 pre-TPVR stents, and presence of a concomitant intervention.

CLINICAL FOLLOW-UP. Of the 530 patients included in this cohort, some follow-up data were provided for 446 subjects (84%) and complete longitudinal outcome data were available for 362 patients (68%) at a median follow-up duration of 372 days (IQR: 176 to 729 days) post-TPVR procedure. Echocardiographic imaging data were available for 310 patients (86% of the follow-up cohort). At follow-up, there was mild or no PI in 98% of the cohort with an evaluation recorded (**Figure 2**). Peak instantaneous and mean PS gradients were 23 mm Hg (IQR: 17 to 31 mm Hg) and 13 mm Hg (IQR: 9 to 18 mm Hg), respectively (**Figure 3**).

During the follow-up period (**Figure 4**), 48 patients (13.3% of the follow-up cohort) underwent post-TPVR cardiac catheterization, cardiac surgery, or both for reasons unrelated to BSI or IE. Catheterization was performed in 34 patients (9.4%), including diagnostic evaluation related to TPVR (35%) or unrelated to TPVR (21%), intervention related to TPVR (18%) or unrelated to TPVR (21%), or implantable cardioverter-defibrillator (ICD) placement (6%). In 4 patients, diagnostic evaluation was performed specifically to evaluate the coronary arteries due to clinical concern for possible TPV-related coronary compression, in the setting of progressive left ventricular systolic dysfunction (n = 3) or new ventricular ectopy (n = 1). A second catheterization procedure was performed in 6 of these 34 patients (18%). Surgical procedures were performed in 23 patients (6.4%), including 9 who underwent both catheterization and surgery. The most common operation was conduit replacement (n = 11), followed by aortic (or truncal) valve replacement (n = 5), AV valve replacement (n = 2), repair of TPV-related vascular injury (n = 2), ICD placement/change (n = 2), and emergent embolectomy for large PA thrombus (n = 1). Of the surgical procedures performed during the follow-up period, 5 cases (23%) occurred within 10 days post-TPVR, including planned tricuspid valve repair (n = 1), conduit replacement (n = 3) and emergent PA thrombectomy (n = 1). Three patients required a second operation during follow-up.

A total of 16 patients underwent reintervention on the TPV during the follow-up period. Factors associated with the need for TPV reintervention are explored in **Table 6**. TPV reintervention was associated with younger age and smaller size at implant, and was more common in patients with truncus arteriosus and PA/IVS. Baseline RVOT diameter was smaller and RV-PA gradient was higher in the

FIGURE 1 Associations Between Radiation Dose and Selected Patient and Procedural Factors



Scatterplots relating radiation dose, in dose area product (DAP)/kg (y-axis), to a series of significantly associated factors, on the x-axis. In each pane, the data have been further stratified by an additional categorical variable. **(A)** Radiation dose is significantly associated with baseline right ventricle (RV) to pulmonary artery (PA) gradient (mm Hg), with individual participants stratified by procedural indication. **(B)** Radiation dose is significantly associated with baseline right ventricular systolic pressure (RVSP) (mm Hg), stratified by the presence or absence of concomitant intervention. **(C)** Radiation dose is significantly associated with participant age (years), stratified by procedural indication. **(D)** Radiation dose is significantly associated with ratio of baseline conduit diameter to implant diameter, stratified by the presence or absence of concomitant intervention.

reintervention group, whereas there was no association with post-TPV implant re-dilation, final RV systolic pressure or RV-PA gradient. Presence of a genetic syndrome and noncardiac diagnosis were more common, although not statistically different, in the reintervention group.

BSI, with suspected or definite IE, was diagnosed in 19 patients (5.2%) during the follow-up period. In 11 patients (58%), treatment was medical alone, whereas in 8 patients (42%), treatment included surgical TPV/conduit replacement. One patient who required ECMO support prior to surgical intervention was not

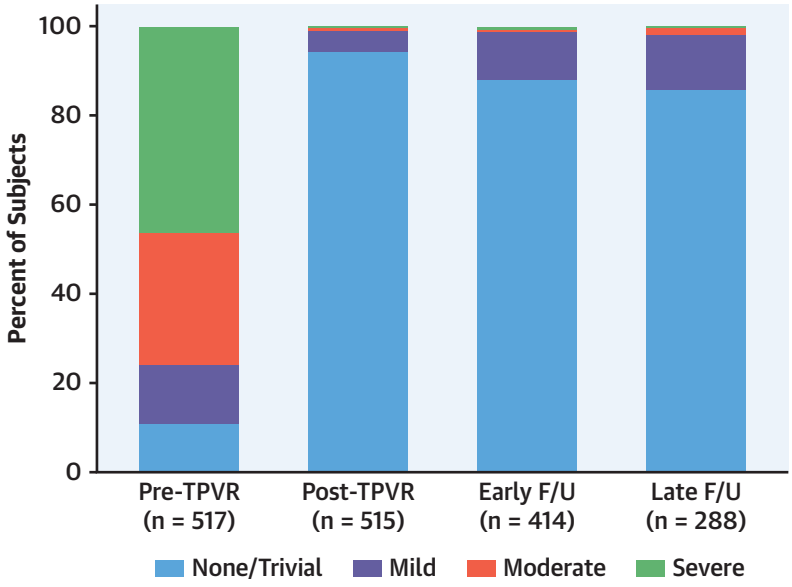
TABLE 5 Multivariable Linear Regression Analysis of Associations With Radiation Dose

Factor	Estimated Coefficient	95% CI	p Value	Exponentiated Coefficient
Age (↑5 yrs*)	0.08	0.05-0.11	<0.001	1.08
Baseline RVSP (↑10 mm Hg†)	0.10	0.07-0.14	<0.001	1.11
≥2 pre-stents implanted	0.42	0.27-0.58	<0.001	1.53
Concomitant intervention	0.44	0.25-0.64	<0.001	1.56

Outcome measure was natural logarithm of radiation dose, reported in DAP/kg ($\mu Gy \cdot m^2/kg$). Model R^2 = 19.4%. *Coefficient reflects the average change for each 5-year increase in age. †Coefficient reflects the average change for each 10-mm Hg increase in baseline RVSP.

RVSP = right ventricular systolic pressure.

FIGURE 2 Longitudinal Assessment of Pulmonary Insufficiency Grade



Stacked bar graphs of pulmonary insufficiency grade, obtained prior to and immediately after the transcatheter pulmonary valve intervention. Early and late follow-up (F/U) echocardiographic assessments of pulmonary insufficiency grade are also displayed. Pulmonary insufficiency is almost eliminated following transcatheter pulmonary valve replacement (TPVR), with the majority of patients demonstrating ≤ mild pulmonary insufficiency at late follow-up.

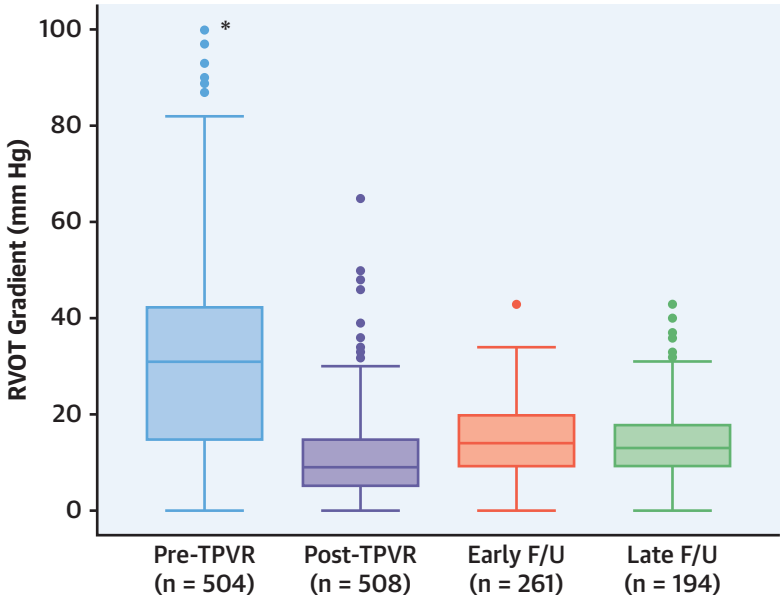
able to separate from mechanical support following conduit surgery, and after a protracted course with multiorgan failure, was the sole endocarditis-related mortality in this report.

DISCUSSION

In this multicenter cohort of 530 TPVR procedures derived from the C3PO-QI registry, we found an overall AE rate of 26.2% and an SAE rate of 13%, with a 0.8% incidence of periprocedural mortality (**Central Illustration**). Radiation dose was considerable, even with respect to congenital catheterization procedures (11). A number of patient and procedural factors were associated with increased radiation dose, including homograft conduit; age; weight; anatomic and physiological measures consistent with pulmonary stenosis; and the presence of an AE, SAE, or non-RVOT concomitant intervention. Implant substrate was significantly associated with risk of SAE, largely derived from a higher risk of hemodynamically insignificant conduit injury in recipients with homograft conduits. Although short-term follow-up revealed excellent TPV function in the majority, the incidence of post-TPVR catheterization and/or cardiac surgery was substantial, reflecting complexities in both the therapy and the underlying CHD population receiving this treatment. This study is among the first to report on procedural adverse events and clinical follow-up in a large multicenter registry of "real-world" patients undergoing TPVR, including a sizable cohort of patients with native RVOT substrate, and the first to explore radiation dose and reintervention in this population.

ADVERSE EVENTS: FACTORS AND LEARNINGS. AE and SAE were common in this large TPV registry cohort and occurred at a similar rate (albeit at the upper end of the range) to what has been reported previously from the device trials (7,9,10). Conduit injuries, which accounted for 29% of all SAE, may be over-represented in this registry compared with prior reports from trials due to the strict definitions used for SAE in the C3PO registry. Even after exclusion of contained conduit injuries from the AE analysis, the rates of AE and SAE remained high, reflecting the complexity of this procedure and heterogeneity of associated complications. Stratification of the cohort by implant substrate demonstrated a few distinctions in SAE rate and types by group. First, SAE was significantly more common in the homograft conduit group; a finding driven by an 8.8% incidence of

FIGURE 3 Longitudinal Assessment of RV-PA Conduit Obstruction

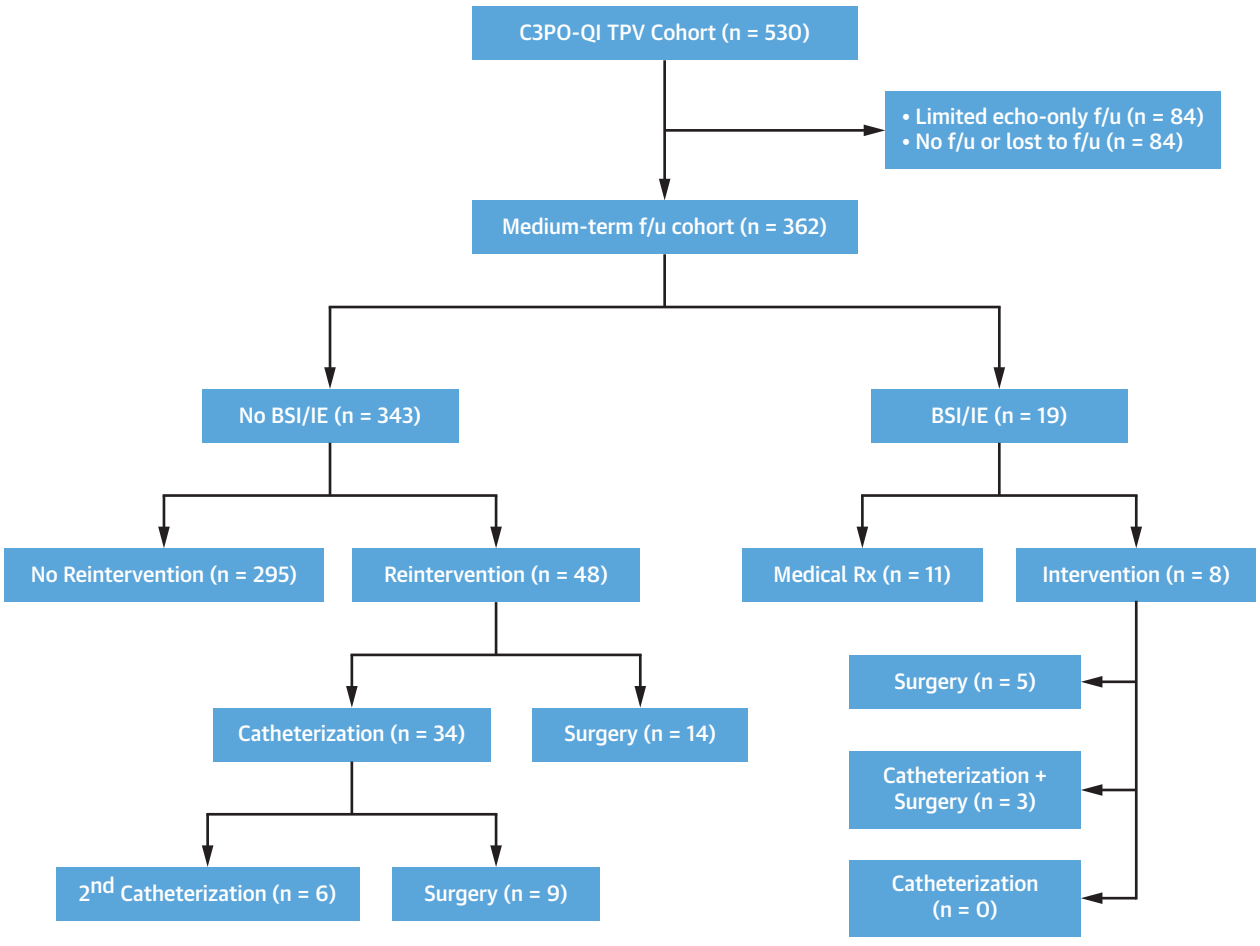


Box and whisker plots of right ventricle to pulmonary artery (RV-PA) conduit gradient (mm Hg) across multiple follow-up points. Displayed are baseline and final RV-PA conduit peak systolic ejection gradients, obtained invasively immediately prior to and after the transcatheter pulmonary valve intervention. *6 patients with pre-transcatheter pulmonary valve replacement (TPVR) gradient >100 mm Hg were not displayed. Noninvasive RV-PA conduit peak instantaneous pressure gradients from early and late echocardiographic follow-up are also depicted. The reduction in RV-PA conduit gradient achieved at catheterization is sustained throughout follow-up. RVOT = right ventricular outflow tract.

conduit injury. Conduit injuries were universally well tolerated in this cohort, suggesting that this SAE specifically is generally of little clinical consequence. Second, although still uncommon, stent- and TPV-related malposition or embolization were more common in native RVOT than other implant substrates (2.8% and 1.4% incidence, respectively), indicative of the larger and often dynamic landing zone present in the native RVOT with PI as the typically dominant procedural indication. TPV malposition/embolization, on the other hand, is a high-risk SAE, necessitating placement of a second TPV in 5 cases and leading to mortality in 1 case. Last, tricuspid valve injury occurred exclusively in native RVOT cases (1.4% incidence; all utilizing Sapien TPVR), reflecting the hazards of utilizing a non-purpose-built delivery system in the right heart. The identification of SAE that cluster in the native RVOT cohort may offer guidance to the operator treating this population with balloon-expandable TPV technology.

Although nonaccess-related vascular injuries and arrhythmias dominated the SAE table, a few rarer events stood out as concerning. Efforts to capture such rare TPV-related events have been made previously but were hampered by self-reporting to the MAUDE database (20). In 5 cases (0.9%), there was either malposition or embolization of the TPV implant necessitating placement of a second TPV. One of these cases resulted in the need for conversion to an open surgical procedure, while another lead to the sole SAE-attributable procedural death. Although the reported periprocedural mortality rate of 0.8% is low, this rate reflects the inclusion of 2 rescue TPV cases, each deemed not to be operative candidates, both of which resulted in mortality. The incidence of periprocedural mortality attributable to AE was 0.2%. Two cases of TPV implantation balloon malfunction each had significant consequences: cardiopulmonary resuscitation, and TPV dysfunction requiring a second implant, respectively. A final case is worth mentioning. Following successful delivery of the TPV to the target landing zone, but prior to implantation, the operator and staff recognized that they had not performed an intraprocedural hold point verifying TPV orientation on the delivery system. Despite having unsheathed the valve, given the potentially catastrophic consequences of implanting a valve in the incorrect orientation, the operator elected to

FIGURE 4 Clinical Follow-Up of the Study Cohort



Flow diagram depicting clinical follow-up of the study cohort. Limited follow-up data were available for 446 patients, whereas complete early follow-up data were available for 362 participants. Clinical outcomes are presented for the follow-up cohort. BSI = bloodstream infection; C3PO-QI = Congenital Catheterization Collaborative Project on Outcomes-Quality Improvement; f/u = follow-up; IE = infective endocarditis; Rx = prescription; TPV = transcatheter pulmonary valve.

remove the TPV, resulting in vascular injury, with subsequent straightforward implantation of a new TPV. These SAEs highlight rare but potentially catastrophic events, some of which may be avoidable, and can provide insight to implanters who may not otherwise encounter such an event in their local practice.

RADIATION DOSE: COMPARISONS AND IMPROVEMENT OPPORTUNITIES. Few prior reports have detailed radiation exposure associated with TPVR. For purposes of comparison, the median radiation dose for TPVR (198 μGy·m^2/kg) was more than double the dose reported for any other congenital transcatheter intervention, including aortic coarctation angioplasty/stent (90 μGy·m^2/kg), balloon aortic valvuloplasty (99 μGy·m^2/kg), balloon pulmonary valvuloplasty (53 μGy·m^2/kg), patent ductus arteriosus device occlusion (37 μGy·m^2/kg) or atrial septal defect device closure (ASD) (34 μGy·m^2/kg) (11). Despite existing and ongoing efforts to limit radiation dose through improvement in operator technique and changes to radiation-generating equipment (11,12,21,22), CHD patients undergoing TPVR will face a lifetime of cumulative ionizing radiation exposure, of which the TPV implantation procedure is a considerable contributor. The need for repeated TPVR, along with the need for additional non-TPVR catheterization procedures in many of these patients, makes limiting radiation exposure particularly important. Not surprisingly, age and weight correlated with indexed radiation dose. More importantly, pre-stent burden (reflecting the degree of stenosis)

and the presence of concomitant interventions were key associations with high dose.

Although the majority of contributing factors reflect the underlying RVOT substrate, and thus, are not readily modifiable, these data could help contribute to innovations in practice. Indeed, existing data from the C3PO registry suggest that modifications in operator practice significantly contribute to reduction in radiation dose (23). Innovations in practice and modifications to device technology may provide the opportunity to reduce radiation dose (and potentially improve outcomes) during TPVR procedures. Delivering multiple pre-stents simultaneously, for example, might reduce radiation exposure without sacrificing stent integrity. Future TPV devices might provide improved radial strength, without sacrificing ease-of-use or deliverability, thus reducing the number of pre-stents necessary. Procedural modifications aimed at reducing radiation dose must be balanced with any potential risks introduced by the respective changes in practice, but population-level data increasingly suggest that radiation-induced risks, including malignancies, cannot simply be ignored (14,15,21).

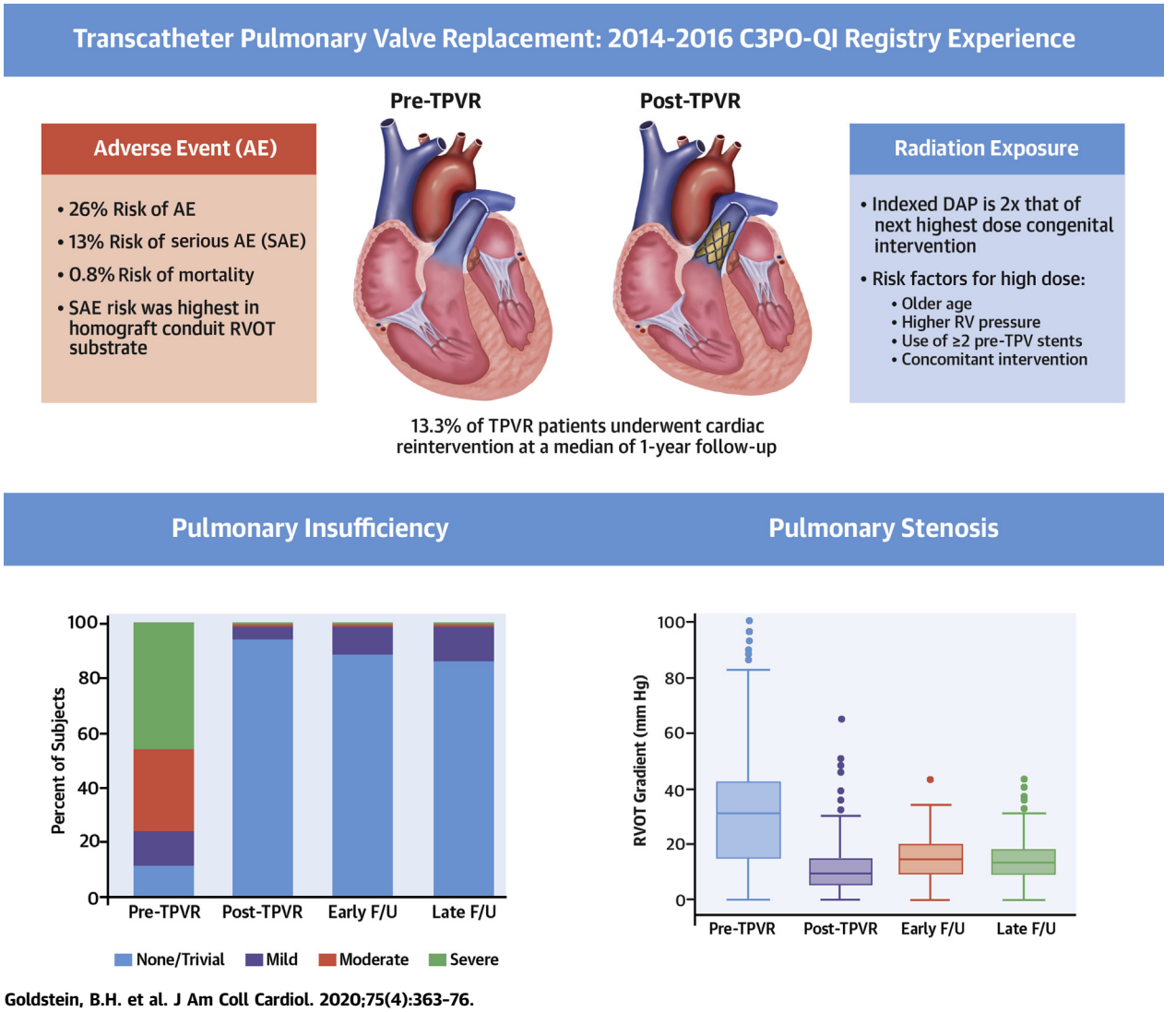
CLINICAL FOLLOW-UP AND REINTERVENTIONS. An important aspect of the C3PO-QI TPV dataset is the inclusion of a follow-up module within the existing C3PO registry framework. Clinical follow-up is critical to describing outcomes in this population, given substantial ongoing hazards, which is unlike many previously studied congenital transcatheter interventions that do not require subsequent procedures (e.g., patent ductus arteriosus closure). Importantly, we were able to obtain limited follow-up from 84% and more complete follow-up from 68% of the cohort. We found that TPV function is maintained through early follow-up, which is consistent with outcomes reported from the clinical trials (8,24). However, we also demonstrated that following TPVR, a significant proportion of the cohort required additional procedures. During a median follow-up duration of just 1-year post-TPVR, >13% of the cohort underwent catheterization and/or cardiac surgery for assessment or treatment of TPV-related (53%) or TPV-unrelated (47%) problems. Although a few of these procedures occurred early after TPVR in the face of complications, inadequate therapy, or pre-planned interventions, most of these procedures occurred post-discharge and reflect either procedural inadequacy (e.g., incomplete relief of PS), nonurgent procedural complications (e.g., vascular injury), or additional cardiac pathology (i.e., ICD placement in tetralogy of Fallot with ventricular tachycardia). Factors found to be associated with TPV reintervention, specifically, include younger age,

TABLE 6 Associations With Reintervention on the TPV

	Reintervention (n = 16)	No Reintervention (n = 350)	p Value
Age, yrs	12.2 (9.5, 17.7)	18.0 (12.7, 27.1)	0.016
Weight, kg	43.5 (29.0, 59.0)	58.5 (44.0, 78.0)	0.008
Cardiac diagnosis			0.002
Tetralogy of Fallot	5 (31)	185 (53)	
Aortic valve disease	0 (0)	27 (8)	
Truncus arteriosus	5 (31)	18 (5)	
Pulmonary valve disease	0 (0)	13 (4)	
PA/IVS	2 (12)	11 (3)	
Double outlet right ventricle	1 (6)	10 (3)	
TGA/CCTGA	0 (0)	14 (4)	
Other	1 (6)	35 (10)	
Not recorded	2 (12)	37 (11)	
Noncardiac diagnosis	4 (25)	37 (11)	0.09
Genetic syndrome	4 (25)	35 (10)	0.08
Prior endocarditis	1 (6)	17 (5)	0.56
RVOT type			0.61
Bioprosthetic	5 (31)	115 (33)	
Homograft	9 (56)	147 (42)	
Native/augmented	2 (12)	82 (23)	
Other	0 (0)	6 (2)	
Procedural indication			0.36
PS	6 (38)	80 (23)	
PI	2 (12)	83 (24)	
Mixed PS/PI	8 (50)	187 (53)	
Nominal conduit diameter	20 (18, 23)	22 (19, 25)	0.15
Existing TPV implant	1 (6)	22 (6)	1.0
Existing RVOT stent	0 (0)	25 (7)	0.61
Baseline RVOT minimal diameter, mm	14 (8, 15)	15 (11, 19)	0.041
Baseline RVSP, mm Hg	70 (56, 78)	60 (45, 74)	0.10
Baseline RV-PA gradient, mm Hg	42 (30, 57)	33 (18, 43)	0.040
Procedure time	183 (108, 249)	174 (137, 228)	0.79
Procedure time (with AE time subtracted)	183 (107, 233)	174 (135, 220)	0.72
Calcification score			0.24
None/trivial	7 (44)	163 (47)	
Mild	1 (6)	70 (20)	
Moderate	5 (31)	63 (18)	
Severe	2 (12)	48 (14)	
Not reported	1 (6)	6 (2)	
Number of pre-stents implanted			0.91
0	3 (19)	89 (25)	
1	5 (31)	111 (32)	
2	6 (38)	101 (29)	
≥3	2 (12)	49 (14)	
Concomitant non-RVOT interventions	4 (25)	69 (20)	0.60
Valve type			0.23
Melody	16 (100)	307 (88)	
Sapien	0 (0)	43 (12)	
TPV implant diameter	21 (18, 22)	22 (20, 22)	0.09
Ratio of baseline to implant diameter	0.64 (0.40, 0.78)	0.70 (0.54, 0.85)	0.09
Post-TPV implant redilation	3 (19)	65 (19)	1.0
Post-TPV RVSP, mm Hg	43 (36, 59)	39 (32, 47)	0.16
Post-TPV RV-PA gradient, mm Hg	10 (4, 19)	10 (6, 15)	0.73
Any AE	7 (44)	87 (25)	0.057
Any SAE	4 (25)	43 (12)	0.14

Values are median (25th, 75th percentile) or n (%).
AE = adverse event; RV-PA = right ventricle to pulmonary artery; other abbreviations as in Table 1.

CENTRAL ILLUSTRATION **Transcatheter Pulmonary Valve Replacement: Adverse Events, Radiation Dose, and Valve Function at Follow-Up**



Goldstein, B.H. et al. J Am Coll Cardiol. 2020;75(4):363-76.

Rates of adverse events and predictors of radiation dose for transcatheter pulmonary valve replacement procedures are displayed. Longitudinal assessment of transcatheter pulmonary valve function, broken down into components (pulmonary insufficiency and stenosis), is also shown. AE = adverse event; C3PO-QI = Congenital Catheterization Collaborative Project on Outcomes-Quality Improvement; DAP = dose area product; F/U = follow-up; SAE = serious adverse event; TPV = transcatheter pulmonary valve; TPVR = transcatheter pulmonary valve replacement.

smaller size, cardiac diagnosis, smaller baseline RVOT diameter, and higher baseline RV-PA gradient. Although post-TPV hemodynamics were not associated with reintervention, TPV implant diameter and ratio of baseline to implant RVOT diameter were both nonsignificantly smaller in the reintervention group, suggesting that an anatomically inadequate result may predict early need for TPV reintervention. It is noteworthy that TPV reintervention occurred exclusively in patients who received a Melody TPV implant. Importantly, this finding was nonsignificant and undoubtedly reflects the different implantation substrates found between valve types in this cohort, rather than early manifestation of differences inherent to the TPV itself. The significant rate of early reintervention implicates problems with

patient selection, which necessarily imposed a substantial economic and procedural burden on affected patients.

A specific concern related to TPVR is the potential for TPV-related coronary artery compression, which prompted 4 patients to undergo late diagnostic coronary angiography in the setting of progressive left ventricular dysfunction or ventricular arrhythmia. Although no patients were found to have coronary compression, the incidence of late invasive reassessment highlights a somewhat new potential problem introduced by the TPVR procedure. The presence of late post-TPVR coronary assessment highlights potential concerns with the observation that 19% of patients did not undergo coronary compression testing at the TPV implant procedure. Finally, concerns related to TPVR and the risk of subsequent BSI/IE persist. Despite extensive investigation, and emerging data on specific risk factors, the risk of BSI/IE remains stable in this population (25–27). In the present C3PO experience, we report an incidence of BSI/IE of 5.2% during a median follow-up period of 1 year. In line with prior publications on this topic, 58% of the affected cohort was successfully treated with medical management alone (25,26). Further investigation including long-term follow-up in this population is mandated in the setting of this ongoing concern.

STUDY LIMITATIONS. This study is limited to the data made available through the C3PO-QI registry, and thus, we were unable to analyze all cases with attempted but unsuccessful TPVR, in which the TPV module was not completed. Therefore, technical success cannot be defined using this dataset, although it has been well-defined previously (7,9,10). Further, due to the nature of the follow-up component in the registry, complete post-TPVR follow-up data were only provided for 68% of the overall cohort, thus constraining the follow-up analysis somewhat. This is due to a combination of patients who were lost to follow-up or received their follow-up care at a non-C3PO participating institution. For these reasons, we were not able to perform certain time-to-event analyses, such as the annualized rate of BSI/IE. Moreover, presentation of these data does introduce the potential for ascertainment and follow-up biases, which would lead to an overestimation of the rate of critical outcomes during follow-up. However, the granular nature of the follow-up data yields important insights—some of which have not been described previously—into the outcomes of this population. Last, although we report TPV data from 2 implant manufacturers, given the presence of asymmetric cohort sizes, differing PVR indications and implant substrates, we have intentionally limited the direct comparison between TPV types.

CONCLUSIONS

In this C3PO-QI registry study, TPVR was demonstrated to be associated with a 26.2% risk of any adverse event and a 13% risk of SAE, including a 0.8% incidence of periprocedural mortality. TPVR procedures were associated with significant radiation exposure, more than double that associated with other congenital transcatheter interventions. Rate and type of SAE differed significantly by implantation substrate. Inclusion of a large cohort of patients with native RVOT revealed critical SAE more likely in that environment, including stent and TPV malposition or embolization and tricuspid valve injury. Clinical follow-up data, an important component of this registry study, demonstrated a post-TPVR catheterization/surgery rate of 13.3% (during a median follow-up of 1 year) among patients without BSI/IE, revealing the often palliative—rather than curative—nature of interventions in the CHD population. Early reintervention on the TPV, and associated factors, may suggest inadequate patient selection. The 5.2% incidence of BSI/IE during short-term follow-up reflects an important ongoing hazard following TPV therapy. Future study in this domain should target reductions in SAE rate, radiation dose, and post-TPVR reintervention rate via improvements in patient selection, procedural technique, and implant technology.

ADDRESS FOR CORRESPONDENCE: Dr. Bryan H. Goldstein, UPMC Children's Hospital of Pittsburgh, 4401 Penn Avenue, 5th Floor Faculty Pavilion, Pittsburgh, Pennsylvania 15224. E-mail: bryan.goldstein@gmail.com. Twitter: @ccrcresearch.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: TPVR mitigates RVOT conduit dysfunction, relieves pulmonary stenosis and insufficiency, and avoids repeated cardiothoracic surgery, but is associated with relatively high radiation exposure and a high rate of adverse events.

TRANSLATIONAL OUTLOOK: More research is needed to identify predictors of adverse events following TPVR and develop technical innovations that reduce the radiation exposure required to achieve successful outcomes.

REFERENCES

1. Bonhoeffer P, Boudjemline Y, Saliba Z, et al. Percutaneous replacement of pulmonary valve in a right-ventricle to pulmonary-artery prosthetic conduit with valve dysfunction. Lancet 2000;356:1403–5.

2. O'Byrne ML, Glatz AC, Mercer-Rosa L, et al. Trends in pulmonary valve replacement in children and adults with tetralogy of Fallot. Am J Cardiol 2015;115:118–24.

3. Cabalka AK, Asnes JD, Balzer DT, et al. Transcatheter pulmonary valve replacement using the Melody valve for treatment of dysfunctional surgical bioprostheses: a multicenter study. J Thorac Cardiovasc Surg 2018;155:1712–24.e1.

4. Whiteside W, Tretter JT, Aboulhosn J, et al. Acute and midterm outcomes of transcatheter pulmonary valve replacement for treatment of dysfunctional left ventricular outflow tract conduits in patients with aortopulmonary transposition and a systemic right ventricle. Circ Cardiovasc Interv 2017;10:e004730.

5. Martin MH, Meadows J, McElhinney DB, et al. Safety and feasibility of melody transcatheter pulmonary valve replacement in the native right ventricular outflow tract: A Multicenter Pediatric Heart Network Scholar Study. J Am Coll Cardiol Intv 2018;11:1642–50.

6. Meadows JJ, Moore PM, Berman DP, et al. Use and performance of the Melody Transcatheter Pulmonary Valve in native and postsurgical, nonconduit right ventricular outflow tracts. Circ Cardiovasc Interv 2014;7:374–80.

7. Armstrong AK, Balzer DT, Cabalka AK, et al. One-year follow-up of the Melody transcatheter pulmonary valve multicenter post-approval study. J Am Coll Cardiol Intv 2014;7:1254–62.

8. Kenny D, Rhodes JF, Fleming GA, 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. J Am Coll Cardiol Intv 2018;11:1920–9.

9. Kenny D, Hijazi ZM, Kar S, et al. Percutaneous implantation of the Edwards SAPIEN transcatheter heart valve for conduit failure in the pulmonary position: early phase 1 results from an international multicenter clinical trial. J Am Coll Cardiol 2011;58:2248–56.

10. McElhinney DB, Hellenbrand WE, Zahn EM, et al. Short- and medium-term outcomes after transcatheter pulmonary valve placement in the expanded multicenter US melody valve trial. Circulation 2010;122:507–16.

11. Cevallos PC, Armstrong AK, Glatz AC, et al. Radiation dose benchmarks in pediatric cardiac catheterization: a prospective multi-center C3PO-QI study. Catheter Cardiovasc Interv 2017;90:269–80.

12. Quinn BP, Armstrong AK, Bauser-Heaton HD, et al. Radiation risk categories in cardiac catheterization for congenital heart disease: a tool to aid in the evaluation of radiation outcomes. Pediatr Cardiol 2019;40:445–53.

13. Glatz AC, Purrington KS, Klinger A, et al. Cumulative exposure to medical radiation for children requiring surgery for congenital heart disease. J Pediatr 2014;164:789–94.e10.

14. Ait-Ali L, Andreassi MG, Foffa I, Spadoni I, Vano E, Picano E. Cumulative patient effective dose and acute radiation-induced chromosomal DNA damage in children with congenital heart disease. Heart 2010;96:269–74.

15. Johnson JN, Hornik CP, Li JS, et al. Cumulative radiation exposure and cancer risk estimation in children with heart disease. Circulation 2014;130:161–7.

16. Cevallos PC, Rose MJ, Armsby LB, et al. Implementation of methodology for quality improvement in pediatric cardiac catheterization: a multi-center initiative by the Congenital Cardiac Catheterization Project on Outcomes-Quality Improvement (C3PO-QI). Pediatr Cardiol 2016;37:1436–45.

17. Delaney JW, Goldstein BH, Bishnoi RN, et al. Covered CP stent for treatment of right ventricular conduit injury during melody transcatheter pulmonary valve replacement. Circ Cardiovasc Interv 2018;11:e006598.

18. Bergersen L, Marshall A, Gauvreau K, et al. Adverse event rates in congenital cardiac catheterization - a multi-center experience. Catheter Cardiovasc Interv 2010;75:389–400.

19. Bergersen L, Gauvreau K, Foerster SR, et al. Catheterization for Congenital Heart Disease Adjustment for Risk Method (CHARM). J Am Coll Cardiol Intv 2011;4:1037–46.

20. Hill KD, Goldstein BH, Angtuaco MJ, Chu PY, Fleming GA. Post-market surveillance to detect adverse events associated with Melody(R) valve implantation. Cardiol Young 2017;27:1090–7.

21. Hill KD, Frush DP, Han BK, et al. Radiation safety in children with congenital and acquired heart disease: a scientific position statement on multimodality dose optimization from the Image Gently Alliance. J Am Coll Cardiol Img 2017;10:797–818.

22. Hirshfeld JW Jr., Ferrari VA, Bengel FM, et al. 2018 ACC/HRS/NASCI/SCAI/SCCT expert consensus document on optimal use of ionizing radiation in cardiovascular imaging-best practices for safety and effectiveness, part 1: radiation physics and radiation biology: a report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. J Am Coll Cardiol 2018;71:2811–28.

23. Nicholson GT, Gao K, Kim SI, et al. Direct physician reporting is associated with reductions in radiation exposure in pediatric cardiac catheterizations. Catheter Cardiovasc Interv 2015;86:834–40.

24. Cheatham JP, Hellenbrand WE, Zahn EM, 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.

25. 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.

26. McElhinney DB, Sondergaard L, Armstrong AK, et al. Endocarditis After Transcatheter Pulmonary Valve Replacement. J Am Coll Cardiol 2018;72:2717–28.

27. Malekzadeh-Milani S, Ladouceur M, Patel M, et al. Incidence and predictors of Melody(R) valve endocarditis: a prospective study. Arch Cardiovasc Dis 2015;108:97–106.

KEY WORDS adverse events, congenital heart disease, dose area product, infective endocarditis outcomes research, tetralogy of Fallot, transcatheter PVR

APPENDIX For supplemental tables, please see the online version of this paper.