

Transcatheter Pulmonary Valve Implantation: A Comprehensive Systematic Review and Meta-Analyses of Observational Studies

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Background—Transcatheter pulmonary valve implantation is approved for the treatment of dysfunctional right ventricle to pulmonary artery conduits. However, the literature is limited because of a small patient population, and it does not reflect changing procedural practice patterns over the last decade.

Methods and Results—A comprehensive search of Medline and Scopus databases from inception through August 31, 2016 was conducted using predefined criteria. We included studies reporting transcatheter pulmonary valve implantation in at least 5 patients with a follow-up duration of 6 months or more. In 19 eligible studies, 1044 patients underwent transcatheter pulmonary valve implantation with a pooled follow-up of 2271 person-years. Procedural success rate was 96.2% (95% confidence intervals [CI], 94.6–97.4) with a conduit rupture rate of 4.1% (95% CI, 2.5–6.8) and coronary complication rate of 1.3% (95% CI, 0.7–2.3). Incidence of reintervention was 4.4 per 100 person-years overall (95% CI, 3.0–5.9) with a marked reduction in studies reporting $\geq 75\%$ pretesting (2.9 per 100 person-years [95% CI, 1.5–4.3] versus 6.5/100 person-years [95% CI, 4.6–8.5]; $P < 0.01$). Pooled endocarditis rate was 1.4 per 100 person-years (95% CI, 0.9–2.0).

Conclusions—Our study provides favorable updated estimates of procedural and follow-up outcomes after transcatheter pulmonary valve implantation. Widespread adoption of pretesting has improved longer-term outcomes in these patients. (*J Am Heart Assoc.* 2017;6:e006432. DOI: 10.1161/JAHA.117.006432.)

Key Words: endocarditis • Melody valve • reintervention • transcatheter pulmonary valve

Transcatheter pulmonary valve implantation (TPVI) was first performed by Bonhoeffer et al¹ in 2000. Bonhoeffer's work led to the development of the Melody Transcatheter Pulmonary Valve (Medtronic Inc, Minneapolis, MN). The Melody valve received US Food and Drug Administration approval under Humanitarian Device Exemption (HDE) in 2010 and Pre-Market Approval in 2015 for the treatment of right ventricular outflow tract (RVOT) conduit dysfunction. Use of the Melody valve has also been reported in off-label, nonconduit cases in both small series^{2,3} and cohort studies including both conduit and native RVOT implantation. More recently, the ES-THV (Edwards Lifesciences LLC, Irvine, CA) has been implanted off-label in the pulmonary valve (PV) position, and the Sapien XT (Edwards Lifesciences LLC, Irvine, California) valve has been approved by the US Food and Drug

Administration for use in dysfunctional right ventricle to pulmonary artery (PA) conduits.

In the last 16 years, multiple reports of outcomes of patients post-TPVI with the Melody valve and ES-THV have been published; however, the largest series is comprised of only 155 patients.⁴ The longest duration of follow-up was a median period of 4.6 years.⁵ In comparison, an estimated 50 000 adults underwent transcatheter aortic valve implantation between 2002 and 2012.⁶ Randomized studies in various populations of adult degenerative aortic stenosis are feasible and have been performed comparing transcatheter aortic valve implantation to surgical aortic valve replacement.^{7–10} Because of patient numbers and disease heterogeneity, randomized trials for TPVI are not feasible; therefore, to improve the body of knowledge of the short- and long-term

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Clinical Perspective

What Is New?

- Pooled data for >1000 patients suggest improving longevity for transcatheter pulmonary valve implantation, especially with universal adoption of pre-stenting and low rates of endocarditis.

What Are the Clinical Implications?

- The study provides updated estimates for procedural risk as well as medium-term outcomes which should facilitate decision making by physicians and patients/families alike.

outcomes post-TPVI, a systematic statistical review and meta-analyses of published observational reports is performed.

Methods

The study was reviewed and approved by the University of Alabama at Birmingham Institutional Review Board (Birmingham, AL).

Search Strategy

We queried the Medline and SCOPUS databases from inception until August 31, 2016 with the following MeSH terms: “Melody valve,” “transcatheter pulmonary valve,” “percutaneous pulmonary valve,” and “transcutaneous pulmonary valve.”

Study Characteristics

All observational studies, including case series and abstracts, were considered. Of these, studies that reported outcomes post-TPVI in at least 5 patients with a minimum of 6 months

follow-up were included. There were instances of multiple publications from the same research group with overlapping patient populations. Caution was exercised in this scenario to carefully select only the publication with largest sample size and longest follow-up. Two authors (A.C., M.A.L.) independently reviewed studies with overlapping authors/institutions, and studies were included by mutual consensus. Figure 1 shows the relevant details of the study selection process.

Data Extraction

Two authors (A.C., J.S.W.) searched all titles and associated abstracts using the described search strategy. Full-text articles for all potentially relevant studies were extracted and reviewed with focus on inclusion criteria and outcome reporting. From these articles, studies were selected for inclusion. The data from these studies were extracted into prestructured forms and reviewed for accuracy and validity by 2 authors (A.C., M.A.L.). Disagreements were resolved with mutual consensus between authors.

Outcome Measures

We analyzed the data primarily to evaluate procedural success of TPVI and to estimate rate of reintervention post-TPVI. Definition of “success” was variable in the studies; however, it was most commonly defined as deployment of a transcatheter pulmonary valve (TPV) with acceptable gradient (<30 mm Hg peak to peak) and regurgitation (≤mild) without a need for surgical conversion before discharge. Reinterventions included catheter-based intervention (balloon angioplasty/valvuloplasty or TPVI) on the TPV or surgical right ventricle to PA conduit replacement.

Secondary outcomes evaluated included procedural complications, survival postprocedure, and incidence of endocarditis in follow-up. Endocarditis was defined as bloodstream

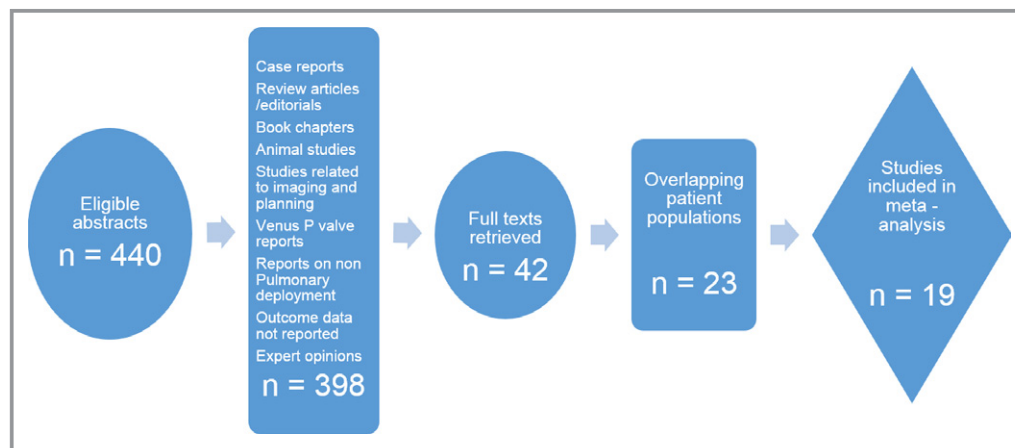


Figure 1. Flow diagram showing selection of studies for analysis.

infection classified in the respective study as possible or definite by the modified Duke criteria.¹¹ Endocarditis events were further analyzed as TPV-specific endocarditis (vegetation visualized on TPV or new dysfunction of TPV) and endocarditis leading to reintervention, explantation, or death. Additionally, a subgroup analysis was performed to ascertain relationship of presenting with need for reintervention. To evaluate effect of presenting, studies were divided into 2 groups—1 with $\geq 75\%$ patients presented before valve deployment and the other with $<75\%$ patients presented. This cut off was chosen to reflect the change in practice in the United States pre- and post-HDE approval of the Melody valve as reported by Armstrong et al.¹²

Statistical Analysis

Systematic and statistical analyses were carried out with Comprehensive Meta-Analysis (version 3; Biostat, Englewood, NJ). Pooled event rates were computed using standard methods. Procedural outcomes are reported as percentages whereas follow-up outcomes are reported as events per 100 person-years (PY) of follow-up. Heterogeneity was assessed with the I^2 test ($I^2 > 50$ and Q-statistic, $P < 0.05$ implying substantial heterogeneity).¹³ Random-effects modeling was utilized to account for studies' heterogeneity and observational nature. Publication bias was assessed using the funnel plot method (Figure 2). All of the P values were 2-tailed, with statistical significance specified at $P < 0.05$ and confidence intervals (CI) computed at the 95% level. The analysis has been reported in accord with the PRISMA guidelines.¹⁴

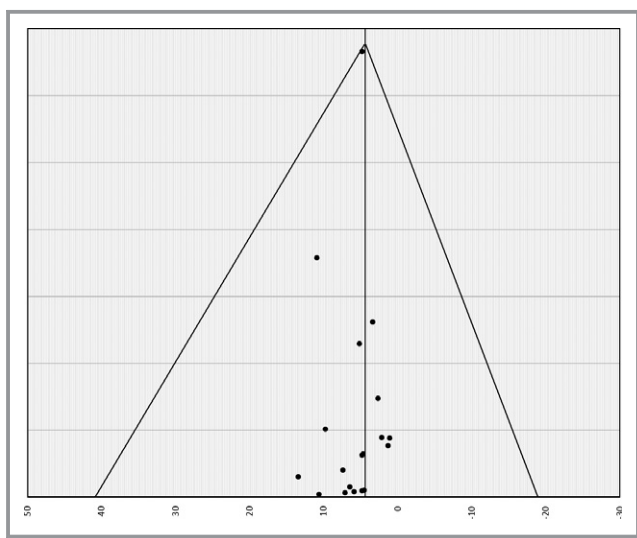


Figure 2. Funnel plot of rate of reinterventions using the SE method (95% CI).

Results

Nineteen observational studies^{2–5,12,15–28} met inclusion criteria and were included in the final analysis. Table 1 illustrates the baseline characteristics of the included studies. A total of 1044 patients underwent attempted TPVI. The pooled analysis yielded a follow-up of 2271 PY. Thirteen studies solely used the Melody valve, 3 reported use of Edwards Sapien or Sapien XT THV, and 3 studies used both Melody and Edwards valve systems. Of the latter 3, Faza et al²¹ reported separate outcomes for Melody and Edwards cohorts. The Edwards cohort had overlapping patients with the study reported by Kenny et al.²⁴ Hence, only the data for the Melody valve cohort were included for analysis from this article. Our data include TPVI attempted with the Melody valve system in 942 patients and Edwards THV system in 102 patients. Seven studies included at least 1 patient with a nonconduit RVOT whereas 2 studies reported solely on TPVI in patients with nonconduit RVOTs.

Patient Selection for TPVI

Eight studies^{4,12,15,16,18,24,25,28} elaborated on the patient cardiac catheterization selection process before attempting TPVI. The pooled estimate of patients considered ineligible for TPVI was 7.7% (95% CI, 4.8–12.2%). In total, 52 of 623 patients were screened out as not suitable for TPVI. Reasons for exclusion included the following: coronary compression on balloon testing (n=18; 2.9%); conduit size not suitable for TPVI (n=18; 2.9%); conduit function better than anticipated on hemodynamic catheterization (n=8; 1.2%), branch PA stenosis (n=2; 0.3%) an exclusion criteria in early trials²⁹; conduit stenosis adequately relieved by angioplasty alone (n=4; 0.6%); surgery needed for other congenital heart defects (n=1; 0.2%); and unspecified (n=1; 0.2%).

Procedural Outcomes

Success and procedural complications

Overall, 1019 of 1044 patients had a successful TPVI, yielding a pooled procedural success rate of 96.2% (95% CI, 94.6–97.4). Pooled procedural mortality was 1.5% (95% CI, 0.8–2.6%). There were a total of 5 procedural deaths. Two deaths were secondary to coronary compression or dissection whereas the other 3 patient deaths occurred when TPVI was utilized in a compassionate salvage procedure and mortality was likely not secondary to an adverse outcome of TPVI.

The adjusted pooled rate for total short-term complications was 10.1% (95% CI, 7.3–13.8). The most

Table 1. Studies Included and Demographic/Clinical Factors of Patients

First Author, Year (Ref)	Patients Considered/ Attempted	Age (y)	Median Follow-up (y)	Valve Used	Primary Pathology				Native RVOT (Yes/No/Only)	Indication		
					TOF/ PA/PS	Ross	TGA/ Truncus	Other		Stenosis	Regurg	Mixed
Wilson, 2015 ²⁷	NA/25	34.0	3.5*	E	17	6	2	0	No	8	7	10
Cheatham, 2015 ²⁸	167/150	19.0	4.5	M	80	31	31	8	No	39	80	31
Cools, 2015 ¹⁹	NA/111	19.3	2.4	M	71	22	18	0	Yes	49	36	26
Jalal, 2015 ²³	NA/10	16.3	0.9*	M	7	0	2	1	Yes	3	2	5
Biernacka, 2015 ¹⁶	42/40	25.4	1.7*	M/E	30	5	4	1	Yes	19	21	0
Borik, 2015 ¹⁷	NA/51	20.2	4.2	M	35	5	10	1	No	NA	NA	NA
Berman, 2014 ¹⁵	25/24	8.0	1.3	M	18	2	5	0	No	5	7	13
Armstrong, 2014 ¹²	120/101	19.9	0.9	M	61	20	28	11	No	16	52	32
Fraisse, 2014 ⁵	NA/64	21.4	4.6	M	35	8	15	6	No	14	7	43
Meadows, 2014 ³	NA/31	24.0	1.3	M	28	0	1	2	Only	3	14	14
Malekzadeh-Milani, 2014 ²	NA/34	26.0	2.6	M	26	2	2	4	Only	18	16	0
Faza, 2013 ²¹	NA/13	20.9	0.5	M	9	0	2	2	No	7	3	3
Odemis, 2013 ²⁶	NA/10	19.2	0.8	M/E	NA	NA	NA	NA	Yes	NA	NA	NA
Butera, 2013 ¹⁸	63/61	24.0	2.5	M	27	9	12	15	No	21	12	30
Haas, 2013 ²²	NA/22	21.7	0.5*	E	13	2	4	3	Yes	2	11	9
Eicken, 2011 ²⁰	NA/102	21.5	1.0	M	61	8	23	10	Yes	36	18	48
Kenny, 2011 ²⁴	36/34	30.3	0.5	E	16	11	1	8	No	15	19	2
Martins, 2010 ²⁵	7/6	19.0	0.7	M	3	0	4	0	No	0	0	7
Lurz, 2008 ⁴	163/155	21.2	2.4	M	94	12	31	18	Yes	61	46	44

E indicates Edwards; M, melody; NA, not applicable; PA/PS, pulmonic atresia/stenosis; Ref, reference number; RVOT, right ventricular outflow tract; TGA, transposition of great vessels; TOF, tetralogy of fallot.

*Mean follow-up.

frequent complication reported was conduit rupture: 4.1% (95% CI, 2.5–6.8). A total of 32 conduit ruptures were reported. The majority of ruptures were treated with covered stent and/or valve deployment. Only 5 required surgical repair. Other frequently observed complications were access-site complications requiring blood transfusion or vascular surgery: 2.8% (95% CI, 1.7–4.6) and dislodgement of stent/valve system: 2.5% (95% CI, 1.3–4.8). Table 2 lists rates of all procedural complications. Notably, despite prescreening for coronary compression in most protocols, 5 patients had a coronary complication from either the bare metal stent used for preenting or the valve system itself (pooled incidence rate, 1.3%; 95% CI, 0.7–2.3).

Surgical conversion for the management of complications occurred in 3.4% of cases (95% CI, 2.3–5.2). Reasons for surgical conversion were stent/valve dislodgement in 9 cases, conduit rupture in 5 cases, coronary compression in 4 cases, obstructed branch PA in 1 case, and stent

compression causing acutely elevated gradient in another case.

Follow-up Outcomes

Death

The adjusted pooled rate for death following discharge after a successful TPVI was 0.6 per 100 PY (95% CI, 0.3–0.9). There were a total of 17 deaths reported. Four of these were attributed to sepsis/endocarditis, 2 were secondary to progressive right ventricle dysfunction despite TPVI, 7 were considered to be unrelated to TPVI, whereas 4 were unexplained and may have been caused by arrhythmia.

Stent fractures

Reporting of stent fractures was not uniform across the studies included. Twelve studies reported on total and significant stent fractures, 2 reported total fractures only,

Table 2. Pooled Estimates for Short-Term Procedural Outcomes

	No. of Studies	Pooled Estimate (%)	I^2	<i>P</i> Value
Procedural success	19	96.2 (94.6–97.4)	0.0	0.48
Total complications	17	10.1 (7.3–13.8)	52.1	0.01
Death	19	1.5 (0.8–2.6)	0.0	0.98
Access complications	16	2.8 (1.7–4.6)	0.0	0.50
Coronary compression/dissection	17	1.3 (0.7–2.3)	0.0	1.00
Conduit rupture	17	4.1 (2.5–6.8)	43.6	0.03
Pulmonary artery perforation/laceration	17	2.1 (1.3–3.5)	0.0	0.85
Stent/valve dislodgement	17	2.5 (1.3–4.8)	38.5	0.05
Surgical conversion	18	3.4 (2.3–5.2)	7.8	0.36

whereas 2 others reported on significant stent fractures only (assumed to be either type 2 or 3 stent fractures per the Nordemeyer classification).²⁹ Pooled incidence of all stent fractures was 4.4 per 100 PY (95% CI, 2.4–6.3) whereas type 2/3 stent fractures were noted in 1.3 per 100 PY (95% CI, 0.5–2.0).

Reintervention

Overall, 4.4 patients required a RVOT reintervention per 100 PY of follow-up (95% CI, 3.0–5.9). Breaking these down, catheter-based reinterventions accounted for 2.7 events per 100 PY (95% CI, 1.7–3.7) whereas adjusted rate for surgical reinterventions was 1.7 per 100 PY (95% CI, 1.2–2.2). There is significant heterogeneity in the studies in this regard, which is negated once we analyze studies after adoption of preenting (Figure 3).^{2–5,12,15–28} In total, 77.5% of reinterventions were done for restenosis, 15.2% for endocarditis, only 1.8% for valve insufficiency, and 5.2% for other indications.

Effect of preenting on stent fractures and reintervention

Studies with $\geq 75\%$ preenting had a much lower total rate of stent fractures (2.3 versus 7.2 per 100 PY; $P < 0.01$). Reintervention was also less frequent in this group: 2.9 per 100 PY (95% CI, 1.5–4.3) as compared with 6.5 per 100 PY (95% CI, 4.6–8.5) for the studies with $< 75\%$ preenting ($P < 0.01$). This difference persisted if we analyze catheter based or surgical reinterventions separately (Table 3).

Endocarditis

Pooled incidence rate of endocarditis in these 19 studies was 1.4 per 100 PY (95% CI, 0.9–2.0). TPV-specific endocarditis (vegetation involving TPV or new TPV dysfunction) and endocarditis requiring reintervention/TPV explantation or

causing death occurred at a rate of 0.6 per 100 PY (95% CI, 0.3–0.9).

Discussion

Our meta-analysis is the first attempt to systematically pool high-quality observational studies to provide an estimate of procedural as well as follow-up outcomes. We report pooled outcomes of more than 1000 patients with a follow-up of 2271 PY. Because 20% of patients with congenital heart disease have RVOT or PV dysfunction,³⁰ many patients undergo surgical RVOT conduit or PV placements during their lifetime and will need revisions with age. TPVI is an attractive option to minimize the need for repeated cardiac surgery for these patients. Although several studies have reported on the safety and feasibility of TPVI with excellent short-term results^{4,18,28} and improvement in cardiopulmonary exercise capacity and quality of life,^{31,32} direct comparisons between surgical valve replacement and TPVI have not been made. European Society of Cardiology guidelines³³ do not distinguish between surgical and catheter interventions. American societies give TPVI a Class IIa recommendation.³⁴ The pooled data from this meta-analysis support TPVI as a highly successful intervention to treat RVOT dysfunction with an acceptable complication profile and low reintervention rate.

Procedural Success and Complications

The procedural success for TPVI is greater than 96%, with a complication rate of 10%. Our pooled estimate for procedural success is consistent with the high rates reported in the US IDE trial²⁸ and postapproval study¹² as well as the larger European studies.^{4,19,20} Failed TPVI procedures were commonly associated with a complication requiring surgical conversion, which occurred in over 3% of cases. We believe

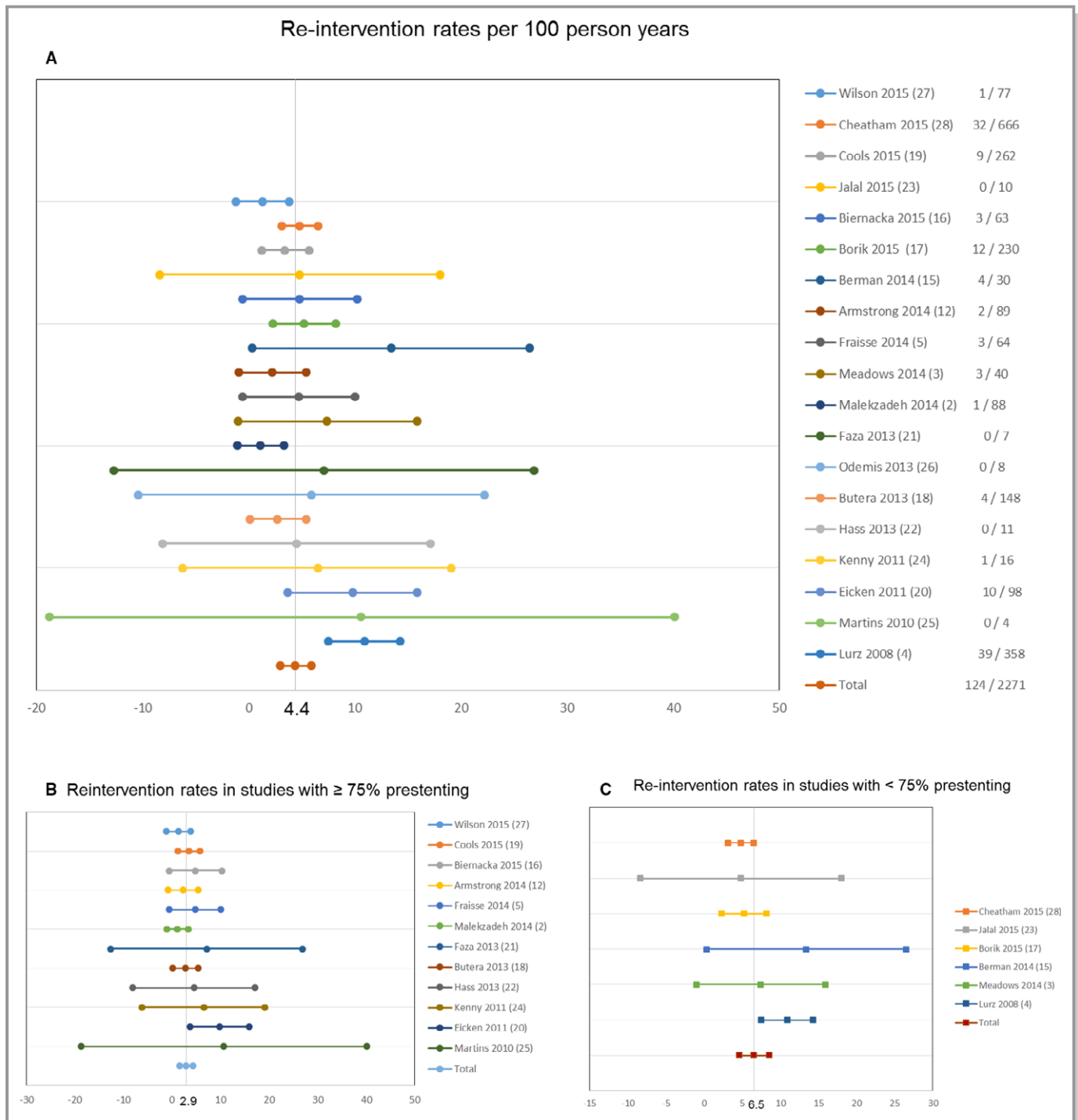


Figure 3. Forest plots depicting reintervention rates in the total pooled sample (A)—individual study event rates are noted in the right column (events/follow-up in person-years); reintervention rates contrasted among studies with <75% (B) and ≥75% prestenotic rates (C).

that procedural experience focusing on decreasing or treating these known complications will further increase TPVI success rates and decrease the frequency of surgical conversion.

Conduit rupture is a significant complication of TPVI. Berman et al¹⁵ reported a very high rate of 20.8% conduit rupture, although this study solely reported on a specific patient

population weighing <30 kg with stenotic homograft conduits. In another series of 99 RVOT interventions, which included 76 TPVI procedures, homografts had a higher frequency of rupture.³⁵ Interestingly, neither conduit size nor type/size of balloon used was associated with risk of rupture. This study classified conduit rupture severity as absent (grade 0), minimal rupture without extension (grade 1), moderate rupture with

Table 3. Pooled Estimates for Outcomes in Follow-up

Parameter	No. of Studies	Events/100 PY	Lower CI	Upper CI	I ²	P Value
Death	19	0.6	0.3	0.9	0.0	0.95
Stent fracture	14	4.4	2.4	6.3	79.7	0.00
Type 2/3 stent fracture	15	1.3	0.5	2.0	53.3	<0.01
Patients requiring reintervention	19	4.4	3.0	5.9	51.4	<0.01
Catheter re-interventions	19	2.7	1.7	3.7	44.7	0.02
Surgical reintervention	19	1.7	1.2	2.2	0.0	0.56
Endocarditis	19	1.4	0.9	2.0	11.9	0.31
TPV specific endocarditis	19	0.6	0.3	0.9	0.0	0.70
Endocarditis requiring explantation/death/reintervention	19	0.6	0.3	0.9	0.0	0.88
Effect of preenting						
Stent fracture						<0.01*
≥75% preenting	8	2.3	0.8	3.7	57.7	0.02
<75% preenting	5	7.2	5.0	9.3	26.9	0.24
Type 2/3 stent fracture						0.01*
≥75% preenting	9	0.6	0	1.2	0.0	0.91
≤75% preenting	5	2.3	1.4	3.2	60.5	0.04
Patients requiring reintervention						<0.01*
≥75% preenting	12	2.9	1.5	4.3	0	0.46
<75% preenting	6	6.5	4.6	8.5	56.5	0.04
Catheter reinterventions						<0.01*
≥75% preenting	12	1.5	0.7	2.3	1.5	0.43
<75% preenting	6	4.4	3.3	5.5	0.0	0.56
Surgical reinterventions						<0.01*
≥75% preenting	12	1.3	0.5	2.0	0.0	0.81
<75% preenting	6	2.2	1.4	3.0	35.7	0.17

PY indicates person-years; TPV, transcatheter pulmonary valve.

*P value for subgroup analysis.

extension but contained and without hemodynamic instability (grade 2), and severe rupture with extension causing hemothorax or hemopericardium and with hemodynamic instability requiring blood transfusion (grade 3). Only 2 of 9 conduit ruptures reported were grade 3, and these were managed without surgery. Similarly, very few of the 32 conduit ruptures in our pooled analysis required surgical conversion, mostly managed with covered stents and/or valve implantation. The pooled rate of conduit rupture (4.1%) is comparable with Armstrong et al,¹² who found an incidence of 5.9%.

Notable other procedural complications with important implications for the TPVI procedure are dislodgement of the stent/valve apparatus and PA perforation. Although these complications can sometimes be managed with catheter techniques, this meta-analysis demonstrates that inability to retrieve or stabilize the dislodged/malpositioned valve or

control PA bleeding results in surgical conversion. Six of the 9 valve dislodgements in our pooled sample were Edwards THV. Although determining whether this finding is significant is beyond the scope of this report, however, off-label implantation of the Edwards THV into patched or native RVOT may be related to increased risk of valve dislodgement. Similarly, we have insufficient information to conclude if nonconduit Melody implants carry a higher risk of the same. Reports of Sapien use for TPVI are from early use of the device and growing familiarity and technical expertise may obviate this difference.

Eligibility for TPVI

Not all patients needing PV replacement are candidates for TPVI. Our pooled estimate of 7.7% of potential TPVI candidates found at the time of the procedure to be ineligible

is comparable to both the US Melody IDE trial (10.2%)²⁸ and the largest European study by Lurz et al (4.9%).⁴ The post-market approval study by Armstrong et al had a higher exclusion rate of 15.8%.¹² It is important to point out that studies elaborating on the patient selection details predominantly did not include native RVOT candidates, hence this estimate should not be extrapolated to nonconduit implants. Because surgical conversion or death are predictable outcomes of coronary compression, this finding during balloon testing is a contraindication to TPVI. As expected, this is the most common reason for patient exclusion from TPVI. The occurrence of coronary compression on balloon testing (raw, 2.9%; pooled estimate, 3.7%) was similar to the 5% reported by Marray et al.³⁶ They studied 404 patients considered for TPVI from 4 large-volume centers included in US IDE trial and found that a large proportion of patients with coronary compression on balloon testing had anomalous coronary artery anatomy (15 of 21). The finding in this meta-analysis supports the practice of careful preprocedural and procedural coronary artery imaging and balloon testing for coronary compression before pretesting or valve implantation.

Branch PA stenosis and unsuitable conduit size were other common reasons for exclusion. Two patients in our pooled sample were excluded because of distal PA stenosis, which would not have been an exclusion criterion in current clinical practice where concurrent intervention could be performed, if indicated. Unsuitable conduit size was another common reason for exclusion. Theoretically, the Melody valve mounted on a 24-mm balloon or the Edwards THV could be implanted in some patients who were excluded secondary to large conduit or RVOT size, potentially decreasing the patient exclusion rate.

Reintervention

There is lack of data on the longevity of the Melody valve. Cheatham et al recently published a rate of 76±4% freedom from reintervention at 5 years²⁸ in the US IDE trial cohort. They found higher rates of reintervention in patients with homografts, without pretesting, a higher post-TPVI RVOT gradient (>25 mm Hg) and preimplantation moderate-to-severe tricuspid valve insufficiency. Our pooled rate of 4.8 per 100 PY also reflects a similar outcome. However, implantation practices have changed over the last decade and now place significant emphasis on pretesting with bare metal stents. Only 10% of cases were pretested in the first tertile of the US IDE trial.²⁸ In comparison, the postapproval study by Armstrong et al observed pretesting in 76 of 101 patients.¹² Similarly, Cools et al and Fraisse et al report pretesting rates of 96.4% and 96.9%, respectively.^{5,19} Schievano et al, in their in vitro modeling study, showed that a stent-in-stent technique decreased mechanical stress on

the TPV stent struts.³⁷ There are increasing data to support that pretesting reduces stent fractures and hence reduces the need of reintervention. A recent meta-analysis investigated the relationship between pretesting and stent fractures pooling data from 5 studies.³⁸ Pretesting was associated with a 2-fold reduction in all stent fractures and a 6-fold reduction in type II/III stent fractures. However, the pooled sample only included 360 patients, of whom 207 were pretested. This study also showed a reduction in RVOT reintervention in pretested patients in a subgroup analysis including 191 patients only with 1 versus 6 reinterventions in pretested and non-pre-stented patients.

With a lack of clinical data regarding pretesting/stent fractures and reinterventions, we chose to analyze the pooled data in a different manner. Adopting Armstrong et al's postapproval study¹² as a reflection of common clinical practice, we divided the studies into 2 groups—≥75% pretesting and <75% pretesting. We found a markedly lower rate of stent fractures (in total and type 2/3) as well as reintervention rates. The reduction in reintervention rates persisted for both catheter and surgical reinterventions. The rates of reintervention in the first group are more comparable to rates reported for surgical conduits and homografts.³⁹ Thus, TPVI seems to be bridging the gap in longevity compared with surgical conduits as practice patterns have become more refined and standardized.

Endocarditis

Bloodstream infections have been recognized as a late complication post-TPVI. Varying rates for endocarditis have been reported in different cohorts of patients. McElhinney et al reported an annualized rate of first episode of endocarditis and TPV-related endocarditis of 2.4% per PY and 0.88% per PY, respectively.⁴⁰ This was derived from 3 patient cohorts in North America and Europe and had a cumulative follow-up of 687.1 PY. Malekzadeh-Milani et al, in their study of 86 patients followed for a mean duration of 23.6±15 months, reported a rate of 5.8% (5 cases).⁴¹ Interestingly, all 5 of these cases could be classified as TPV-related endocarditis. Buber et al reported a rate of 9.5% (14 cases) in their 147 patient study over a median follow-up period of 19 months.⁴² Whereas vegetations were only noted on 4 valves, all 14 cases had a new elevation in RVOT gradient. The pooled rates for endocarditis and TPV-specific endocarditis estimated in our study are considerably lower, with a cumulative follow-up of over 2200 PY.

It is thought that TPVI in a smaller conduit is a risk for endocarditis given a higher residual gradient.^{40,43} Also, a majority of cases reported have been associated with predisposing conditions, including noncompliance with antibiotic prophylaxis regimen with dental or other invasive

procedures, and concomitant bacterial infection.^{4,18,40} Role of aspirin discontinuation has also been reported.⁴¹ In retrospective comparisons of Melody valve versus surgical RVOT conduits, Melody valves have been noted to have a higher rate of endocarditis.^{44,45} The difference is pronounced when comparing Melody valves with homografts, but not for Contegra bovine valved conduit, suggesting possible tropism of micro-organisms to the bovine material used in making the Melody and Contegra valves.⁴⁵

Limitations

The primary study limitations are inherent to the meta-analysis study design. Systematic pooling of different observational studies with differences in baseline characteristics, anatomic substrate, sample sizes, implantation techniques, valve type, and different follow-up durations introduce imprecision in the results because of heterogeneity. Many studies included have small sample sizes and follow-up durations and may lead to falsely low outcome rates, especially for endocarditis. There are variations in reporting how many patients were screened but considered ineligible for TPVI. Under-reporting of outcomes has to be taken into account given that all of the data included are observational. We concede that there is variability in how data are presented in each study, criteria for implant, and adverse event reporting are also nonuniform. There may be under-reporting of endocarditis, especially in the earlier studies. Moreover, there has been refinement of the procedure and improved outcomes as operators have become more experienced. It should be kept in mind that results from this analysis cannot be extrapolated to long-term outcomes.

Because TPVI is now considered standard of care, randomized controlled trials proving the safety and efficacy of TPVI versus surgical right ventricle to PA conduit or PV implantation are not feasible. Furthermore, small sample size limitations in congenital heart disease makes pooling of multiple observational studies a logical approach to increase the evidence to support interventional therapies and outcomes. Thus, in spite of the inherent limitations, this meta-analysis can clarify extensive and sometimes conflicting data by systematic organization and aggregation of available observational data. We hope that the pooled estimates can be used as a “worst-case scenario,” especially given that it includes a significant number of patients from the early years of TPVI.

Conclusion

In our systematic review and meta-analyses pooling studies reporting TPVI outcomes on conduit as well as nonconduit

RVOTs with Melody and Edwards THV systems, TPVI was found to have an outstanding procedural success rate with an acceptable complication profile and low need for surgical conversion. We also demonstrate corroborative evidence of decrease in stent fractures and RVOT reinterventions with increase in adoption of pretesting with bare metal stents. Our analysis reports lower rates of infective endocarditis and TPV-related endocarditis than previously reported; however, this finding should be evaluated with caution, given the chance of under-reporting of events in observational data and the potentially catastrophic effects of TPV endocarditis. More experience needs to be gained with nonconduit RVOT TPVI procedures as well as with using the newer generations of Edwards Sapien XT and Sapien 3 systems to draw concrete conclusions about the same.

Disclosures

None.

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