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One-Year Follow-Up of the Melody Transcatheter Pulmonary Valve Multicenter Post-Approval Study

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ABSTRACT

OBJECTIVES This study sought to confirm that the short-term hemodynamic effectiveness of the Melody transcatheter pulmonary valve (TPV) (Medtronic, Inc., Minneapolis, Minnesota) achieved by real-world providers is equivalent to the historical results established in the initial 5-center Investigational Device Exemption trial.

BACKGROUND TPV replacement has been used to treat right ventricular outflow tract (RVOT) conduit dysfunction for >10 years. The Melody TPV received U.S. Food and Drug Administration approval in 2010 as a Humanitarian Use Device.

METHODS Patients with dysfunctional RVOT conduits were entered in this prospective, nonrandomized study at 10 centers. The primary endpoint was acceptable hemodynamic function at 6 months post-implantation, defined as a composite of RVOT echocardiographic mean gradient ≤30 mm Hg, pulmonary regurgitation less than moderate as measured by echocardiography, and freedom from conduit reintervention and reoperation.

RESULTS Cardiac catheterization was performed in 120 patients for potential implantation of the Melody TPV; of these, 100 patients were implanted, with a 98.0% procedural success rate. There were no procedure-related deaths. Acceptable hemodynamic function at 6 months was achieved in 96.7% of patients with evaluable data (87.9% of the entire implanted cohort), with results maintained through 1 year. No patient had moderate or severe pulmonary regurgitation after implantation. No patient required catheter reintervention in the first year after implantation, and 2 patients required reoperation for conduit replacement. The rate of freedom from TPV dysfunction was 96.9% at 1 year.

CONCLUSIONS This first prospective, real-world experience with the Melody TPV in the United States demonstrates continued high procedural success, excellent short-term TPV function, and low reintervention and reoperation rates at 1 year. (Melody Transcatheter Pulmonary Valve Post-Approval Study; NCT01186692) (J Am Coll Cardiol Intv 2014;7:1254–62) © 2014 by the American College of Cardiology Foundation.

Congenital heart defects involving the right ventricular outflow tract (RVOT), such as tetralogy of Fallot with pulmonary atresia and truncus arteriosus, as well as patients who have undergone a Ross operation, are often treated with surgical placement of a right ventricular-to-pulmonary artery (RV-PA) conduit. RVOT conduits develop stenosis and/or insufficiency over time due to the

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development of calcification, intimal proliferation, and graft degeneration. Conduit stenosis and insufficiency place a pressure and volume load, respectively, on the right ventricle, predisposing the patient to the development of right ventricular (RV) systolic and diastolic dysfunction, dilation, and tricuspid regurgitation. These changes in the right ventricle in turn can lead to arrhythmias, exercise intolerance, and risk of sudden death (1). Restoring RVOT function can result in improved RV size and exercise tolerance, as well as decreased risk of arrhythmias (1,2). Multiple RVOT conduit reoperations to restore RVOT function are needed over the course of a patient's lifetime due to conduit degeneration (3), and subsequent conduits can have shorter durations of freedom from failure compared with original conduits (4).

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Transcatheter pulmonary valve (TPV) implantation with a stent-mounted bovine jugular venous valve was first reported in an RVOT conduit in 2000 as a means of delaying eventual surgical conduit replacement (5) and has more recently been reported elsewhere (6–8). The Melody TPV (Medtronic, Inc., Minneapolis, Minnesota) was studied initially in the United States in a 5-center Investigational Device Exemption (IDE) protocol (no. G050186). A total of 150 patients with dysfunctional RVOT conduits were enrolled between January 2007 and January 2010. Patients who underwent Melody TPV placement experienced significant improvement in pulmonary regurgitation (PR), RV systolic pressure, and New York Heart Association (NYHA) functional class with relatively uncommon serious adverse events (SAE) (9). The Melody TPV was then approved by the U.S. Food and Drug Administration as a Humanitarian Use Device in January 2010 to treat dysfunctional circumferential RVOT conduits that were ≥16 mm at initial implantation. Humanitarian Use Device approval required that a post-approval study be performed to confirm the results of the IDE trial in 10 U.S. centers to which the therapy was new. We describe here the initial results of the post-approval study with 1-year outcomes.

METHODS

STUDY DESIGN. The U.S. Melody Transcatheter Pulmonary Valve Post-Approval Study is an ongoing, prospective, nonrandomized, historically controlled study designed to confirm that the short-term hemodynamic effectiveness of implantation of the Melody TPV in 100 patients with dysfunctional RVOT conduits is noninferior to the results obtained in the IDE trial. Patient selection was based on specific criteria used in the IDE trial but did not include the age (5 years of age and older) and weight (≥30 kg) limitations. Key inclusion criteria included patients eligible for a Melody TPV (dysfunctional conduit ≥16 mm when originally implanted: moderate or greater regurgitation and/or stenosis with a mean RVOT gradient ≥35 mm Hg by transthoracic echocardiography). Key exclusion criteria included use in the aortic or mitral position and active endocarditis. All patients meeting selection criteria were offered enrollment consecutively until the maximal number of implants (15 per center) was reached. It is possible that a few eligible patients may not have agreed to study enrollment because participation was voluntary. At each center, participating implanters were proctored on ~5 implants before study implantations were started. A variable number of commercial implantations may have been performed before the initiation of the study or during the study period in patients who were either not eligible to participate or who elected not to participate. Enrollment ranged from 3 to 21 patients per site, with implantations ranging from 3 to 15 per site. The primary objective was to confirm that the short-term hemodynamic effectiveness of implantation of the Melody TPV achieved by real-world providers is equivalent to the historical control established in the 5-center IDE study. Evaluation time points were discharge, 6 months and 1 year post-implantation, and annually for 5 years or until TPV explantation. SAE were defined according to International Organization for Standardization 14155 (10). The study was approved by the institutional review board at each institution, and written informed consent was obtained from patients and/or guardians before the catheterization. The U.S. Melody Transcatheter Pulmonary Valve Post-Approval Study was designed and funded by the study sponsor (Medtronic, Inc.), which was responsible for selection of the study sites, monitoring of data, management of case report forms, and statistical analyses. The study investigators made the decision to write this paper and agreed on the submitted version.

OUTCOME MEASURES. The primary outcome measure of acceptable valve hemodynamic function at 6 months post-implantation was determined for patients with the TPV implanted for >24 h and as a composite of the following: mean RVOT gradient ≤30 mm Hg by continuous-wave Doppler recording on transthoracic echocardiography, severity of conduit

ABBREVIATIONS AND ACRONYMS

IDE = Investigational Device Exemption

NYHA = New York Heart Association

PR = pulmonary regurgitation

RV = right ventricular

RVOT = right ventricular outflow tract

RV-PA = right ventricular–to–pulmonary artery

SAE = serious adverse event(s)

TPV = transcatheter pulmonary valve

TABLE 1 Secondary Outcome Measures

Safety
Serious procedure-related adverse events
Serious device-related adverse events at 6 months post-implantation
Incidence of serious device-related adverse events over the follow-up period
Freedom from death (all-cause, procedural, and device related)
Efficacy
Procedural success
TPV implanted in desired location, and
RV-PA peak-to-peak gradient <35 mm Hg, and
No more than mild PR by angiography, and
Free from explantation at 24 h post-implantation
Freedom from stent fracture
Freedom from reintervention on the TPV
Freedom from RVOT conduit reoperation
Freedom from TPV dysfunction
No more than mild PR by echocardiography
Mean RVOT gradient ≤40 mm Hg
Free from reintervention and RVOT conduit reoperation
Clinical utility
Changes in NYHA functional class

NYHA = New York Heart Association; PR = pulmonary regurgitation; RV-PA = right ventricular-to-pulmonary artery; RVOT = right ventricular outflow tract; TPV = transcatheter pulmonary valve.

TABLE 2 Demographic Data and Conduit Characteristics of 120 Patients Undergoing Catheterization (N = 120)

Weight, kg	59.4 ± 21.7 (18.6-119.0)
Sex	
Male	79 (66.0)
Female	41 (34.0)
Age, yrs	19.9 ± 9.7
Diagnosis	
Tetralogy of Fallot	47 (39.2)
Absent pulmonary valve	5 (10.6)
With pulmonary stenosis	22 (46.8)
With pulmonary atresia	19 (40.4)
Atrioventricular canal	1 (2.1)
Truncus arteriosus	18 (15.0)
Ross operation	20 (16.7)
D-Transposition of the great arteries	6 (5.0)
L-Transposition of the great arteries	4 (3.3)
Isolated pulmonary stenosis	4 (3.3)
Pulmonary stenosis and ventricular septal defect	3 (2.5)
Pulmonary atresia/intact ventricular septum	2 (1.7)
Pulmonary atresia and ventricular septal defect	5 (4.2)
Other	11 (9.2)
RVOT conduit type	
Homograft	79 (65.8)
Biological	23 (19.2)
Bioprosthetic valve	16 (13.3)
Synthetic	2 (1.7)
RVOT conduit size, mm (N = 119)	21.4 ± 3.6
Bioprosthesis (n = 16)	24.4 ± 3.2
Conduit (n = 103)	20.9 ± 3.4
No. of previous surgical conduits	
1	61 (50.8)
2	49 (40.8)
3	8 (6.7)
4	2 (1.7)
No pre-existing RVOT conduit stent	99 (82.5)

Values are mean ± SD (range) or n (%).
RVOT = right ventricular outflow tract.

regurgitation less than moderate by transthoracic echocardiography, and freedom from RVOT conduit reoperation or catheter reintervention. Based on the results of the IDE trial, to achieve noninferiority, the performance goal for acceptable hemodynamic function was set at 75%. Secondary outcome measures were intended to characterize the safety, efficacy, and clinical utility of the Melody TPV (Table 1).

ECHOCARDIOGRAPHY. Conduit mean gradients were measured by tracing the border of the spectral continuous-wave Doppler recording. PR was categorized into none, trace, mild, moderate, and severe by assessing the width of the color Doppler jet compared with the conduit width and by the diastolic color flow reversal in the pulmonary arteries (11,12). All echocardiographic data were site-reported.

CARDIAC CATHETERIZATION PROCEDURE. Patients meeting entry criteria underwent cardiac catheterization while under either general anesthesia or conscious sedation. The peak-to-peak systolic gradient was calculated as the difference in systolic pressure between the RVOT and the main pulmonary artery. The RV/aortic pressure ratio was also calculated. Angiography performed in the conduit was used to measure the narrowest diameter of the conduit at the site of intended implantation. Assessment of coronary artery anatomy and conduit angioplasty was performed at the discretion of the implanter. Concomitant interventional procedures were allowed. The size of angioplasty balloons, balloon waist size for implant, pre-stenting of the RVOT, and post-implantation dilation were determined by the implanter.

FOLLOW-UP EVALUATION. Clinical assessment, transthoracic echocardiography, and chest radiography were performed at discharge, 6 months, and 12 months post-implantation at each implantation center. At the 6-month visit, chest radiography included fluoroscopy.

STATISTICAL ANALYSIS. Descriptive statistics were used to summarize the patient population and

procedural and clinical follow-up, and echocardiographic data. The number and percentage of patients are provided for categorical variables, and continuous variables are presented as mean ± SD or median (minimum, maximum). The exact method was used to test the one proportion hypothesis of non-inferiority. The Student paired *t* test was used to evaluate the change in tricuspid regurgitation jet velocity and mean RVOT gradient from pre-implantation to 6 months and from pre-implantation to 12 months. The Wilcoxon signed rank test was applied to evaluate change in tricuspid regurgitation and PR from pre-implantation to 6 months and from pre-implantation to 12 months. A p value <0.05 was regarded as statistically significant, except in the multiple comparisons of the tricuspid and pulmonary valve hemodynamics. In these cases, the Bonferroni method was used to adjust for the multiple comparisons, and the statistical significance was set at p value <0.0125. Kaplan-Meier analyses were performed for time-to-event data, and Peto's method was used to calculate the SE for freedom from an event. Factors associated with TPV dysfunction could not be assessed appropriately due to the small number of events; therefore, Cox regression was not performed. Statistical analyses were performed using SAS software version 9.2 (SAS Institute Inc., Cary, North Carolina).

TABLE 3 Baseline Clinical Status and Right-Heart Hemodynamics of the 100 Patients Undergoing Attempted Melody TPV Implantation (N = 100)

NYHA functional class*	
I	34 (34.0)
II	49 (49.0)
III	14 (14.0)
IV	1 (1.0)
Primary indication	
Stenotic	16 (16.0)
Regurgitant	52 (52.0)
Mixed	32 (32.0)
RVOT mean gradient by echocardiography, mm Hg (n = 97)	33.3 ± 14.1
Median (range)	34.0 (5.6–70.0)
Maximal TR velocity by echocardiography, m/s (n = 70)	3.8 ± 0.8
Median (range)	3.9 (1.0–5.2)
Pulmonary regurgitation by echocardiography	
None	2 (2.0)
Trace	6 (6.1)
Mild	7 (7.1)
Moderate	40 (40.4)
Severe	44 (44.4)
Catheterization	
Peak RV-PA gradient, mm Hg	36.2 ± 17.2
Median (range)	37.5 (3–110)
RV/aortic pressure ratio	0.7 ± 0.2
Median (range)	0.7 (0.3–1.4)

Values are n (%), mean ± SD, and median (range). *Could not be assessed in 2 patients.

RV = right ventricular; TR = tricuspid regurgitation; other abbreviations as in Table 1.

RESULTS

PATIENTS. From July 2010 to July 2012, 120 patients (79 male, 65.8%) with a mean age of 19.9 ± 9.7 years (range 5 to 45 years) were enrolled and underwent catheterization for potential implantation of a Melody TPV. Demographic data and conduit characteristics are listed in Table 2.

PROCEDURAL OUTCOMES. Of the 120 patients undergoing catheterization, TPV implantation was not attempted in 19 patients due to the risk of coronary artery compression (n = 6), conduit not suitable for implant (n = 4), criteria for intervention not met during catheterization (n = 4), relief of conduit stenosis by angioplasty (n = 3), need for surgical repair of another heart condition (n = 1), and risk of branch pulmonary artery stent compression (n = 1).

TPV implantation was attempted in 101 patients but was aborted in a 19.9-kg patient due to distal branch pulmonary artery perforation leading to self-resolved pulmonary hemorrhage. Implantation was performed in 100 patients, and their baseline clinical status and right-heart hemodynamics are summarized in Table 3. The femoral venous approach was used in 87 patients (87%) and internal jugular venous in 13 patients (13%). Concomitant procedures were performed in 84 of the catheterizations (84%), including 76 procedures with conduit pre-stenting (46 with single stents and 30 with multiple stents), 13 with balloon angioplasty of a branch pulmonary artery, and 9 with ≥1 stents placed in the branch pulmonary arteries. In patients undergoing TPV implantation, the original conduit diameters ranged from 16 to 30 mm, and the outer diameters of bioprosthetic valves ranged from 19 to 31 mm, based on manufacturer sizing.

Procedure-related SAE occurred in 16 of the 120 patients (13.3%) undergoing catheterization, with 2 SAE occurring in 1 patient (Table 4). Confined conduit tear was the most common of the procedural SAE, occurring in 5% of catheterizations. All cases were determined to be SAE because intervention was required, and all were treated successfully with covered stents.

The procedural success rate (see Table 1 for definition) for the 101 implantation attempts was 98% (n = 99). In addition to the previously mentioned

TABLE 4 Procedural and Device Related SAE in 120 Patients Undergoing Catheterization

No. of Patients	Complication	Outcome
	Procedural SAE	
6	Contained conduit tear	Resolved with covered stent
1	Distal PA perforation	Self-resolved
1	Lower extremity peripheral neuropathy from access site hematoma	Self-resolved
1	Pulmonary edema from mitral stenosis and fluid given during procedure	Resolved with IV diuretics during additional hospitalization
1	Fever	Resolved with 5 days of IV antibiotics
1	Minor hemorrhage at access site after discharge	Resolved with compression and hospitalization
1	Deep venous thrombosis	Resolved with warfarin
1	Common femoral artery occlusion due to closure device	Resolved with vascular surgery
1	Paravalvular leak	Resolved with second Melody placement
1	Pulseless ventricular tachycardia 15 h post-implantation	Resolved with cardioversion and lidocaine
1	Ventricular tachycardia during procedure	Resolved with cardioversion
1	Coronary compression with myocardial ischemia	Resolved with surgical conduit replacement
	Device-Related SAE	
3	Endocarditis	All resolved with antibiotics; 1 patient had surgery for aortic and pulmonary valve replacement after 2 episodes of endocarditis and aortic aneurysm
1	Sepsis	Resolved with antibiotics
1	Major stent fracture (no pre-stent)	Surgical conduit replacement
1	Pulmonary embolism	Resolved with medical therapy
1	Palpitations	Resolved spontaneously during hospitalization for observation
1	Atrial flutter	Resolved with cardioversion

IV = intravenous; PA = pulmonary artery; SAE = serious adverse events.

patient with the pulmonary hemorrhage, 1 of the implanted patients who had a Ross operation experienced left main coronary artery occlusion during TPV implantation, despite the fact that there was no coronary compression on balloon testing. In the remaining 99 patients, there was no more than mild TPV insufficiency by angiography, and no one had a RV-PA peak gradient ≥35 mm Hg at catheterization.

6-MONTH AND 1-YEAR FOLLOW-UP. Clinical status and functional capacity. All patients implanted >24 h and with follow-up data were alive at 1 year. One patient withdrew from the study at 58 days post-implantation, and 1 patient was lost to follow-up after the 6-month visit.

The percentage of patients in NYHA functional class I increased from 35% at baseline to 89% at 1 year (Figure 1). In 1 patient with NYHA functional class III symptoms and protein-losing enteropathy pre-implantation, class IV symptoms developed after implantation due to progression of the severe enteropathy and not to TPV dysfunction.

Hemodynamic results and reintervention. Of the 99 patients implanted for >24 h, acceptable TPV hemodynamic function at 6 months was confirmed in 87 patients (96.7% of those with evaluable echocardiographic data and 87.9% of entire cohort), with 87 patients having a mean RVOT gradient ≤30 mm Hg and no patient having moderate or worse PR, needing catheter-based reintervention, or requiring surgical RVOT conduit replacement. This was significantly better than the study performance goal of 75% ($p < 0.0001$). Adequate 6-month echocardiographic data were missing for 8 patients in addition to data for the aforementioned patient who withdrew before the 6-month visit.

Acceptable TPV hemodynamic function at 1 year was confirmed in 82 patients (94.3% of those with evaluable echocardiographic data and 82.8% of the entire cohort), with 82 patients having a mean RVOT gradient of ≤30 mm Hg and no patient having moderate or worse PR (Figure 2). Two patients underwent surgical conduit replacement after the 6-month visit, one for endocarditis and the need for concomitant aortic valve and root replacement and the other for major stent fracture with severe stenosis. No patient required additional catheter-based intervention. The 1-year rate of freedom from catheter- or surgery-based reintervention was 98.0% and from TPV dysfunction, was 96.9%, as shown in Figure 3A. The echocardiographic mean RVOT gradient decreased from 33.3 ± 14.1 mm Hg pre-implantation to 15.0 ± 9.9 and 15.1 ± 7.1 mm Hg at 6 months and 1 year, respectively. More than 84% of the patients had moderate or severe PR at baseline, but no patient had moderate or severe PR after implantation, including at 1 year. The majority of patients had no PR (Figure 2). In addition to improvement in PR, echocardiographic tricuspid regurgitation improved significantly from baseline to 6 months and 1 year ($p < 0.0001$).

SERIOUS ADVERSE EVENTS. Aside from procedural events, device-related SAE occurred in 8% of patients in the first year of follow-up (Table 4). There were no deaths in the first year.

Endocarditis. Endocarditis was one of the most common SAE, occurring in 3 patients in the first year post-implantation with a 1-year freedom from endocarditis rate of 97.0% (Figure 3B). The cases were not thought to be procedure related because they occurred 50, 56, and 132 days post-implantation, and only 1 case was shown to have Melody TPV involvement by echocardiography. Two cases were due to *Staphylococcus aureus* and 1 to variable coccobacilli. All patients were treated successfully with

antibiotics, but 1 patient underwent surgery for RVOT conduit replacement and concomitant aortic valve and root replacement. A fourth patient had enterococcal sepsis 58 days after implantation but did not meet the modified Duke criteria for endocarditis diagnosis. The patient was successfully treated with 6 weeks of antibiotics.

Stent fracture. During follow-up, stent fracture occurred in 7 patients, with only 1 patient requiring reintervention (defined as major stent fracture) due to severe stenosis without PR. The patient with the major stent fracture did not have a pre-stent placed in the homograft. The 6 patients with minor stent fractures were all pre-stented, and none had TPV dysfunction at 6-month or 1-year follow-up.

DISCUSSION

This post-approval study of the Melody TPV substantiates the findings of the 5-center IDE trial by 10 additional U.S. centers. Both studies demonstrated the safety and hemodynamic effectiveness of the TPV throughout the first year after implantation.

PROCEDURAL SUCCESS. The procedural success rate in this study was 98.0%, which was comparable to the 100% success rate achieved in the IDE trial (9). Our study, however, showed procedure-related SAE in 13% of the 120 patients undergoing catheterization, which was higher than the 6% seen in the IDE trial. For the IDE trial, patient enrollment was limited to those ≥5 years and ≥30 kg, and concomitant interventions, such as conduit bare metal stenting and branch pulmonary artery stenting, were not allowed in the initial 35 patients enrolled. Our study did not have any limitations on concomitant procedures, age, or weight. In fact, 84% of our patients underwent concomitant interventional procedures, of which 78% were stenting procedures, whereas only 41% of the IDE patients underwent concomitant procedures. Additional interventions lengthen the procedure and offer more potential for complications or adverse events to occur. Furthermore, there was no age or weight limit in our study, and 1 of the 2 patients in whom implantation was unsuccessful due to pulmonary hemorrhage before implantation would have been too small to enter the IDE trial. Detailed patient information such as the presence of comorbidities, complete hemodynamics, and other predictors for risk stratification were not collected in our study to allow a fair comparison of the patient populations, although 15% of patients in both studies were in NYHA functional classes III and IV. Given the procedural restrictions and rigors of the

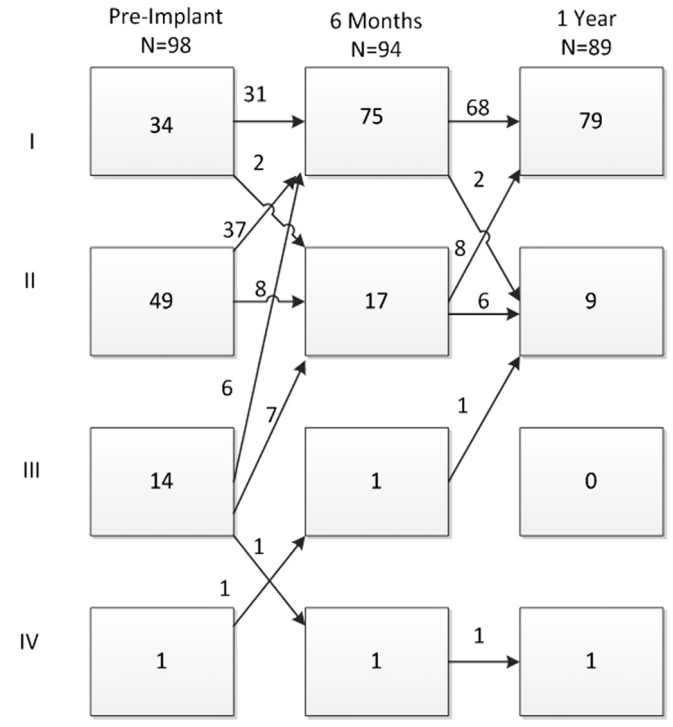

FIGURE 1 New York Heart Association Functional Class

Flow diagram depicting the number of patients in each functional class and changes in class from pre-implantation to the 6-month and 1-year follow-up evaluations.

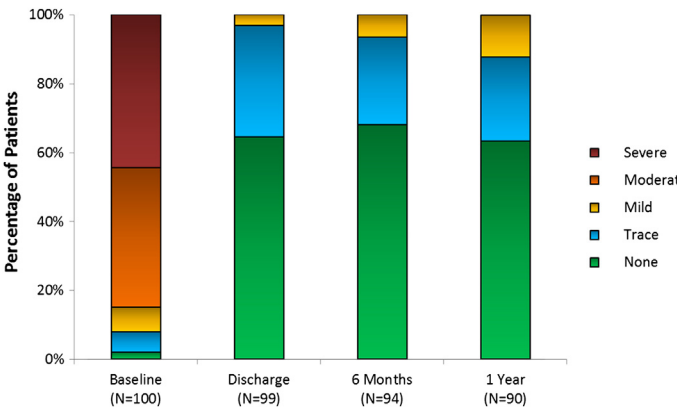

FIGURE 2 Pulmonary Regurgitation Grades

Bar graph showing the distribution of echocardiographic pulmonary regurgitation at baseline, discharge, 6 months, and 1 year post-transcatheter pulmonary valve implantation.

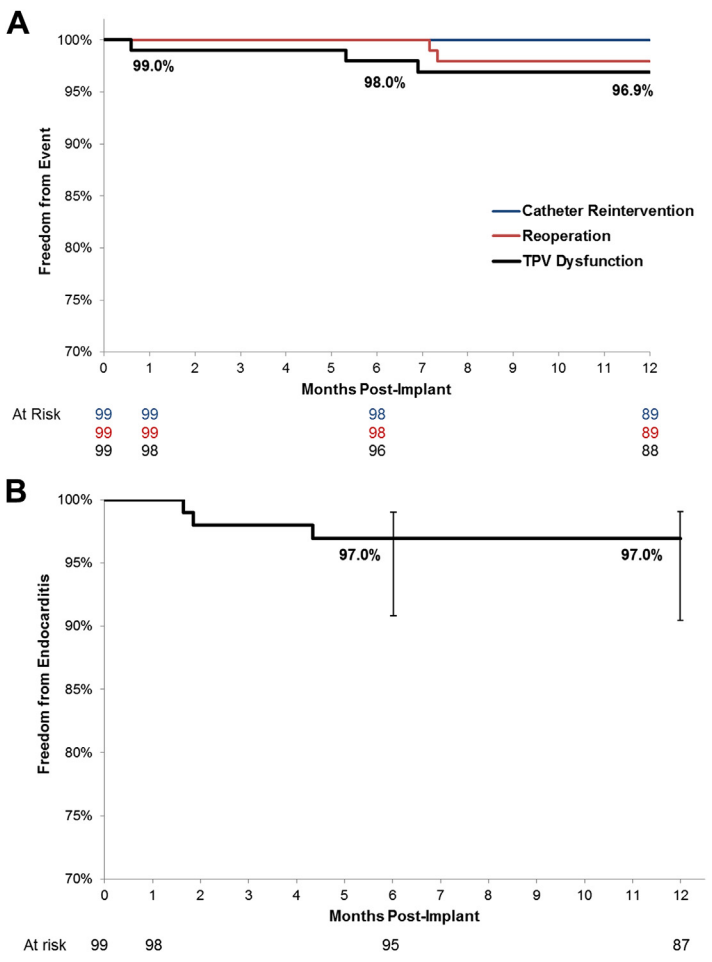

FIGURE 3 Freedom From Catheter Reintervention, Reoperation, and TPV Dysfunction and Endocarditis

Kaplan-Meier curves showing freedom from catheter reintervention, reoperation, and transcatheter pulmonary valve (TPV) dysfunction **(A)** and endocarditis **(B)**.

IDE study, it is expected that the real-world study would have more procedural complications. Indeed, our procedural SAE rate was comparable to the 14% in the Italian multicenter prospective study in which there was also 1 patient who required emergency surgery (13).

Coronary arteries can run in close proximity to RVOT conduits, and pre-implantation testing with imaging of the coronary arteries during balloon inflation in the conduit is recommended. Six patients (5%) who underwent catheterization in our study did not undergo implantation due to the risk of coronary compression. This is comparable to 4.7% in a large retrospective study by Morray et al. (14), which included the IDE trial patients. One patient status post Ross operation in our study did have compression of the left main coronary artery on delivery of the Melody TPV despite negative results on balloon testing and no evidence of coronary compromise after placement of 2 bare-metal stents in the RVOT homograft conduit. The patient required immediate placement of a left ventricular assist device and transfer to the operating room for surgical RVOT conduit removal. This demonstrates the limitations of balloon testing, as it may not always be possible to completely predict the space effect of the implanted Melody TPV with an angioplasty balloon. Coronary compression from Melody TPV placement has been described and can be catastrophic (15–17).

FOLLOW-UP RESULTS. Although there were more procedural SAE in our study compared with the IDE trial, the TPVs in our study had equivalent function and fewer reinterventions. The hemodynamic outcome measured in the IDE study was freedom from TPV dysfunction (no more than mild PR by echocardiography, mean RVOT gradient ≤40 mm Hg, and freedom from reintervention and RVOT conduit reoperation). The rate of freedom from TPV dysfunction at 1 year was 93.5 ± 2.4% in the IDE trial compared with 96.9 ± 1.8% in our study. Although direct statistical comparisons cannot be made between the 2 studies, presumably the higher dysfunction in the IDE trial was due to more reinterventions with 11 of 124 (8.9%) implanted patients requiring catheter- or surgery-based reintervention as opposed to 3 of 100 (3.0%) in our study. The higher reintervention rate in the IDE trial was due to a higher incidence of stent fracture with freedom from all stent fracture rates of 83.7 ± 3.7% at 1 year (9) and 77 ± 4% at 14 months (18) versus 92.7 ± 2.8% at 1 year in our study. McElhinney et al. (18) found that implantation of the Melody TPV within any intact pre-stent was associated with longer freedom from diagnosis of stent fracture, TPV dysfunction, and RVOT reintervention. Our study population had a higher incidence of concomitant pre-stenting of the RVOT (76%) than in the IDE trial (35%), which did not allow concomitant procedures in the first 35 patients (9). The improved performance of the Melody TPV in our study may reflect the real-world experience of the use of the valve over time and incorporation of techniques such as pre-stenting to avoid early valve dysfunction.

RVOT conduit mean gradients by echocardiography decreased from 33.3 ± 14.1 mm Hg at baseline to 15.0 ± 9.9 mm Hg at 6 months in our study, which compares favorably with 33.4 ± 15.0 mm Hg and 20.0 ± 8.6 mm Hg, respectively, in the IDE trial. PR decreased from moderate or severe in 81% of IDE

patients and 84% of Post-Approval Study patients to no more than mild in any patient in either study at 1 year (9).

Endocarditis was not reported in the short- and medium-term outcomes of the IDE trial (9) but did occur in 10 of 150 IDE patients all >6 months post-implantation (442.7 patient-years of follow-up), as reported by McElhinney et al. (19) in the combined results of the 3 prospective North American and European Melody TPV studies, which included this Post-Approval Study. Meeting endocarditis criteria in that combined study only required that a patient be febrile and have a positive blood culture with an organism known to cause endocarditis. Evidence of vegetation or valve dysfunction was not required. The combined study showed an annualized rate of a first episode of 2.4% (95% confidence interval: 1.4% to 3.8%) per patient-year with a median duration from implantation to diagnosis of 1.3 years (range, 50 days to 4.7 years) (19). Using the definition of endocarditis based only on fever and positive blood culture, 4 patients in our study would meet these criteria with infection occurring at 50, 56, 58, and 132 days post-implantation. When considering only those with TPV vegetation or new or progressive TPV dysfunction in addition, then the annualized rate for a first episode was 0.88% in the combined study (95% confidence interval: 0.32% to 1.9%) per patient-year. The true incidence of endocarditis in surgically placed RVOT prostheses in patients with congenital heart disease is unknown, and available data are based on case series, which show a total incidence ranging from 0.5% to 5.9% and may be fraught with underreporting (19). The incidence of endocarditis in our present study is comparable to the incidence seen in left heart prosthetic valves of 3.1% at 12 months (20). It is unknown whether there are unique features of the RVOT conduit, such as calcification, or of the Melody TPV itself that may predispose to endocarditis, but extenuating circumstances, such as a history of endocarditis, open oral or skin lesions, or preceding dental cleaning were present in nearly two-thirds of the cases in the combined study (19).

STUDY LIMITATIONS. First, a core lab was not used to review the hemodynamic and echocardiographic data. These data were interpreted at the individual institutions. Second, due to the small number of events of TPV dysfunction, a Cox regression analysis to identify factors associated with TPV dysfunction could be biased and was not performed. Lastly, our study did not have age, weight, or concomitant intervention limitations, as the IDE trial did, making direct comparisons of procedural success and SAE between the 2 studies difficult.

CONCLUSIONS

This is the first prospective, multicenter post-approval study in the United States of the Melody TPV in the treatment of dysfunctional RVOT conduits. It confirms the strong performance of the Melody TPV achieved by real-world providers with results comparable to those of the U.S. IDE trial. Although continued follow-up is needed to determine the significance and risk factors for stent fractures and endocarditis in this population, the study met its primary objective of noninferiority to the IDE trial results at 6 months. With a high procedural success rate, excellent hemodynamic function at 6 and 12 months, and relatively low rates of SAE, the Melody TPV remains a less invasive alternative to surgical RVOT conduit replacement. Delaying surgery may help to decrease the total number of open heart surgeries required in a lifetime.

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