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Comparison of the Investigational Device Exemption and Post-Approval Trials of the Melody Transcatheter Pulmonary Valve

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ABSTRACT

Objective: We compared 5-year outcomes of transcatheter pulmonary valve (TPV) replacement with the Melody TPV in the Post-Approval Study (PAS) and the Investigational Device Exemption (IDE) trial.

Background: As a condition of approval of the Melody TPV after the IDE trial, the Food and Drug Administration required that a PAS be conducted to evaluate outcomes of TPV replacement in a "real-world" environment. The 5-year outcomes of the PAS have not been published, and the IDE and PAS trials have not been compared.

Methods: The cohorts comprised all patients catheterized and implanted at 5 IDE sites and 10 PAS sites. Differences in trial protocols were detailed. Time-related outcomes and valve-related adverse events were compared between the 2 trials with Kaplan-Meier curves and log-rank testing.

Results: 167 patients (median age, 19 years) were catheterized and 150 underwent TPV replacement in the IDE trial; 121 were catheterized (median age, 17 years) and 100 implanted in the PAS. Freedom from hemodynamic dysfunction (p=0.61) or any reintervention (p=0.74) over time did not differ between trials. Freedom from stent fracture (p=0.003) and transcatheter reintervention (p=0.010) were longer in PAS, whereas freedom from explant (p=0.020) and TPV endocarditis (p=0.007) were shorter. Clinically important adverse events (AEs) were reported in 14.0% of PAS and 7.2% of IDE patients (p=0.056); the incidence of any particular event was low in both.

Conclusions: Hemodynamic and time-related outcomes in the PAS and IDE trials were generally similar, confirming the effectiveness of the Melody TPV with real-world providers. There were few significant complications and limited power to identify important differences in

AEs. The lack of major differences in outcomes between the two studies questions the usefulness of mandated costly post-approval studies as part of the regulatory process for Class III medical devices.

KEY WORDS

pulmonary heart disease, tetralogy of Fallot, transcatheter pulmonary valve replacement

INTRODUCTION

In the United States, high-risk (class III) medical devices are typically approved by the Food and Drug Administration (FDA) based in part on clinical trials performed in a clearly defined patient population at a limited number of centers. For uncommon disease processes, including those involving children, the number of patients enrolled in regulatory trials is usually small as well. In an effort to make the device available clinically while simultaneously accruing additional information on safety and efficacy, the FDA often recommends a post-approval study (PAS) in conjunction with device approval (1-4). Although there has been concern about the adherence to these recommendations and the cost and value of PAS in general (1-3,5), the concept of continued prospective surveillance without delaying approval, with the aim of expediting device availability without compromising safety, has merit. In addition, outcomes reported in regulatory trials do not always reflect the broader experience with a therapy once it becomes more widely available (5-15), and PAS have the potential to provide novel safety and efficacy insights in an expanded "real world" environment.

The investigational device exemption (IDE) trial for the Melody transcatheter pulmonary valve (TPV; Medtronic, Minneapolis, MN) began in 2007 and enrolled its final patient in early 2010, around the same time that the FDA granted a humanitarian device exemption to market the valve commercially. A total of 171 patients were enrolled in the IDE trial, and 150 had a Melody valve implanted with a high rate of technical success, generally excellent outcomes, and few serious adverse events (AEs) (15-17). The FDA stipulated that Medtronic collect post-approval data through continued follow-up of the IDE cohort and by performing a 100-patient PAS at centers that did not participate in the IDE trial, which was initiated concurrently with broader commercial utilization of the Melody valve. The 1-year results of the PAS trial were published in

2014 (18), and all implanted patients in that trial have now completed the full 5-year follow-up protocol.

Since its approval, the Melody TPV has been widely incorporated into the management of patients with congenital heart disease after surgery on the right ventricular outflow tract (RVOT). Several registry or single-center studies have been published (19-24), and a review of the Manufacturer and User Facility Device Experience (MAUDE) database identified several low-frequency complications that were not seen in the IDE trial (25). There is a growing body of evidence about how real-world practice and outcomes compare to the initial regulatory trial experience, but few studies with extensive long-term follow-up (26-28). The IDE trial necessarily engendered a learning curve as the study protocol evolved to include patients with bioprosthetic valves and to allow pre-stenting to protect against stent fracture of the Melody valve, and as investigators gradually came to understand better how to prepare conduits for TPV implant. There were likely other, less obvious areas of evolution related to technical and patient-selection factors.

Although IDE and PAS data have been combined, along with another prospective study performed in Europe and Canada, to address important questions related to Melody TPV therapy (29-32), potential differences between study cohorts and outcomes have not been assessed. Now that 5-year post-implant data are complete for both the IDE and PAS trials, which is nearly unprecedented for implantable cardiovascular devices, there is an opportunity to understand how enrollment, procedural practices, and outcomes may have changed during the evolution from the regulatory trial to the post-approval commercial setting and to assess the information gained from the PAS beyond what was learned in the IDE trial. Thus, we undertook the present study to compare the IDE and PAS trial cohorts directly.

MATERIALS AND METHODS

The data, analytic methods, and study materials are owned by the sponsor (Medtronic) and will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. Both the IDE and PAS trials were registered at clinicaltrials.gov (NCT00740870 and NCT01186692). The statistical analysis plan for the analyses reported here were not preregistered.

Patients

This study included all patients enrolled in the prospective multicenter IDE and PAS trials, which were described previously (15-18). Implanted patients were followed until study exit: the earliest of death, TPV explant, or completion of the prescribed follow-up duration (10 years for the IDE trial and 5 years for PAS). For this analysis, IDE follow-up data were only included through 5 years to facilitate direct comparison with PAS.

Trial Protocols

The specific inclusion and exclusion criteria, evaluations, and outcomes of the 2 trials are summarized in Supplemental Table I. The IDE initially included 3 sites and a target of 30 implants, which were eventually increased to 5 sites and 150 implants, while the PAS trial included 10 sites and targeted 100 implants. In addition, the IDE trial underwent a series of amendments from the initially implemented version through the version under which enrollment was completed. The amendments were made primarily to increase the number of allotted patients, but also included changes in inclusion criteria, evaluations, and transition from premarket to postmarket approval. The PAS trial differed from the IDE protocol in several ways but underwent only minor amendments after initial approval. One important difference was the

use of a core laboratory for echocardiogram interpretation in the IDE but not PAS. Institutional review board/ethics committee approval was obtained from each center in both trials, and patients/guardians provided written informed consent.

Data Coding and Modification

Data analyzed for this study were current as of the database lock dates (June 2, 2016, for IDE; November 7, 2017, for PAS), which were beyond the 5-year follow-up windows for all patients in both trials. For the purposes of analysis, selected variables were categorized in a consolidated format from the original coding by one of the authors. For example, existing conduit/valve type was recoded to differentiate more clearly between different types of biological valves or conduits. Similarly, indications for TPV reintervention, which could include multiple codes in the database, were simplified into 3 categories: stenosis or pulmonary regurgitation (PR) with stent fracture, endocarditis, and stenosis/PR without stent fracture or endocarditis. For procedural AEs, cases with multiple related or sequential events were collapsed into the highest severity event for the purposes of reporting frequency. Also, the free-text descriptions of reported AEs were retrospectively reviewed and categorized according to the event details.

Statistical Analyses

Categorical data were reported as frequency (%), and continuous data as median (quartiles 1, 3). Comparisons of echocardiographic outcomes between studies were based on site-reported data because only the IDE study utilized a core laboratory. Kaplan-Meier curves and log-rank test were used to compare freedom from valve-related AEs between patients in the IDE and PAS trials who were implanted for >24 hours, with a significance level of <0.05. Time-related outcomes were defined according to the PAS protocol and included freedom from hemodynamic

dysfunction (RVOT mean gradient >30 mm Hg, PR ≥ moderate, or conduit reintervention), any TPV reintervention (surgical or catheter-based), explant, and TPV endocarditis, as defined previously (32). A competing risk analysis was performed as described in the Supplemental Methods. Analyses were performed using SAS software, version 9.4 (Cary, NC). Data analyses were performed by SW. The lead (JK) and senior (DBM) authors had full access to all data in the study and take responsibility for its integrity and the data analyses.

RESULTS

Patients

A total of 171 patients were enrolled in the IDE trial (from 25 to 47 per center), and 131 were enrolled in PAS (from 3 to 21 per center). The disposition of patients from enrollment through 5 years is summarized in Supplemental Figure 1. Four patients enrolled in the IDE trial did not undergo catheterization (1 withdrew consent, 2 did not meet echocardiographic inclusion, 1 had better-than-anticipated ventricular function on magnetic resonance imaging) (17), while 10 patients enrolled in PAS did not undergo catheterization because they did not meet echocardiographic criteria for implant. Details of and comparison between patients enrolled in the 2 trials are summarized in Table 1.

TPV implant was not attempted in 17 of 167 catheterized patients in the IDE trial (10%) and 20 of 121 (17%) in PAS (p=0.11) for reasons summarized in Table I. The implant procedure was aborted in 1 PAS patient due to distal branch pulmonary artery perforation (18), resulting in 100 patients receiving a TPV. Favorable hemodynamics (either with or without conduit angioplasty) was more often listed as a reason for not implanting a valve in PAS than IDE patients.

Details of implanted and catheterized patients are summarized in Table II and Supplemental Table II, respectively. A small number of patients in the PAS trial weighed <30 kg at the time of TPV replacement (TPVR), whereas the IDE protocol excluded patients <30 kg. The proportion of patients with a stented bioprosthetic valve was higher in PAS than IDE, which excluded patients with a non-conduit bioprosthetic valve until midway through the trial. Similarly, a larger proportion of enrolled patients were in New York Heart Association (NYHA) class I in PAS than IDE, but highly symptomatic patients (classes III, IV) were similarly represented in both trials.

Procedural Factors

Procedural details for the 2 trials are summarized in Table III. The most notable difference was the frequency of RVOT pre-stenting before TPV implant, which was performed in 36% of implanted patients in the IDE trial and 76% in PAS. Venous access was more often through the jugular vein in PAS than IDE but was a small subset of both cohorts. There were several other procedural differences between trials, all related in part to differences in protocols. Pre-dilation of the conduit, required in the IDE trial, was performed in only 85% of PAS patients. Conversely, RVOT pre-stenting, which was not permitted during the initial portion of the IDE study, was performed in a majority of PAS but only one-third of IDE patients. Covered stents were used infrequently in both trials, only 2 IDE patients and 8 PAS patients. Other procedures, branch pulmonary artery interventions in particular, were performed more often in PAS than IDE, which did not permit planned concomitant interventions.

Outcomes

<u>Procedural outcomes</u>

Acute hemodynamic outcomes were similar in both trials (Table III). Procedural AEs differed between trials in several respects. Among catheterized patients, there were 31 unique

serious procedural AEs, 12 in 12 IDE trial patients (7.2% of patients) and 19 in 17 PAS patients (14% of patients; p=0.056 vs IDE) Supplemental Table III. Conduit rupture or dissection, which was not specifically defined in either trial protocol, was reported in 3 of 167 catheterized IDE patients (1.8%) and 7 of 121 (5.8%) PAS patients. No patients reported to have a conduit rupture or dissection in the PAS cohort developed hemothorax or hemodynamic consequences of the tear, while 2 IDE patients reportedly had hemothorax, 1 without hemodynamic consequences. Other than conduit injury, there were very few serious AEs in either trial, and sample sizes were too small to discern robust AE rates or differences between trials.

Time-Related Outcomes

Freedom from hemodynamic dysfunction, stent fracture, any reintervention, explant, and endocarditis curves are depicted in Figures 1-3. There were no significant differences between trials in freedom from hemodynamic dysfunction or any reintervention. Freedom from stent fracture and from catheter-based reintervention were longer in the IDE cohort, while freedom from explant and from TPV endocarditis were shorter in the PAS cohort. Forty-one IDE patients and 22 PAS patients underwent reintervention on the Melody valve, as summarized in Supplemental Table IV. Eight IDE patients and 2 PAS patients underwent a surgical reintervention 8 days to >7 years after an initial transcatheter reintervention. Among the 34 patients diagnosed with endocarditis (17 IDE and 17 PAS), 17 were treated successfully with only medical therapy. Endocarditis treatment is summarized in the Supplemental Results.

Competing outcome curves for death and any reintervention or explant are depicted in Supplemental Figures 2 and 3. The only difference between the IDE and PAS trials by Fine-Gray subdistribution hazard analysis was in the cumulative incidence of TPV explant (Supplemental Table V).

Hemodynamic and clinical outcomes were similar in the 2 trials, with few patients having significant PR or NYHA class III or IV symptoms (Figure 4). Only 10 patients were reported to have moderate (n=8, 2 in IDE and 6 in PAS) or severe (n=2, both in PAS) PR at any point during follow-up. This included 3 patients who developed PR acutely (n=2 in PAS) or subacutely (n=1 in PAS) after endocarditis, 2 who developed PR >2 years after an episode of endocarditis, 1 who developed PR 3 years after angioplasty of the Melody valve (PAS), and 4 (n=2 in IDE and n=2 in PAS) who developed PR without preceding endocarditis or TPV reintervention.

DISCUSSION

The prospective IDE and PAS Melody valve trials are landmarks in the arena of class III medical devices developed for pediatric/congenital disease, prospectively following patients for 10 and 5 years, respectively, after implant. These studies offer unprecedented prospective, mid- to long-term follow-up data in a small, complex patient population, without which our understanding of the benefits and drawbacks of this device would be substantially limited. Nevertheless, these trials represent the earliest clinical experience with the Melody valve in the United States and were beset by limitations that included challenging protocol constraints, evolving understanding of procedural factors, and the inevitable learning curve effects. As a result, the findings of the IDE and PAS trials likely do not reflect contemporary practice. The current study was undertaken to assess if and how the PAS cohort and outcomes may have differed from the IDE trial to provide insight into interpretation of the data from both and to understand more clearly the additive value of the PAS experience in our collective understanding of TPVR therapy. This structure was motivated in part by considerations about the regulatory approach to obtaining “real world” data for high-risk medical devices.

Trial Protocols

There were several differences in the trial protocols, driven by a variety of factors. Some differences, such as removal of required exercise cardiopulmonary testing and magnetic resonance imaging for PAS, precluded comparative evaluation. Others, such as modification of inclusion criteria and allowance of concomitant procedures, reflected the clinical features and needs of this population as well as sufficient comfort with the TPVR procedure based on the IDE trial to liberalize its application. Perhaps the most impactful difference between the protocols was the allowance of pre-stenting in the PAS trial. Although this change was implemented in an amendment to the ongoing IDE trial, pre-stenting was not fully adopted until the latter portion of the study (16,29), and, ultimately, only 36% of implanted IDE patients had a pre-stent placed, compared with 76% of PAS patients. A longer collective experience with TPVR during the PAS trial and differences in experience with this and related procedures prior to the trials, such as simple conduit stenting, may have contributed to practical differences that would be difficult to discern in this analysis.

Patient Populations and Procedural Factors

There were several modest differences in the IDE and PAS trial populations, some of which were related to protocol differences and some of which may have reflected a better understanding of how to apply the technology after the IDE trial and device approval. There were significantly more NYHA class I patients in PAS than IDE, which had higher thresholds for inclusion of asymptomatic patients—a higher gradient and more severe PR were necessary to meet the stenosis and PR indications. Similarly, mixed stenosis and PR was more common in PAS than IDE, also due to different thresholds for “obstruction” and “PR” among NYHA class I patients in the IDE trial. A handful of patients weighed <30 kg in the PAS trial, whereas the IDE

trial required a minimum weight of 30 kg; this factor may have contributed to a higher incidence of jugular venous access, which tends to be more common and favorable in small patients.

Many of the procedural differences between trials were related in part to protocol constraints or changes. The most obvious of these was the utilization of pre-stenting, which was initially prohibited in the IDE trial and did not catch on fully until the latter part of that trial. Other small differences may have been related to patient selection or clinical decision-making, such as the number of patients who were enrolled and underwent catheterization but had sufficient hemodynamic improvement from conduit angioplasty alone that a TPV was not implanted (1 in the IDE trial, 5 in PAS). Other more nuanced procedural and practical differences, such as what type of guidewires or pre-dilation balloons were used or how they were used, the extent of and specific approaches to conduit preparation, how patients were counseled before and after the procedure, etc., would not be evident in the data collected as part of these trials, so the insights provided by the current study in this regard are limited.

Outcomes

In general, patients who underwent TPVR in the PAS trial had acute outcomes similar to those in the IDE study, thus reinforcing findings of the IDE trial without new major insights. In both studies, procedural AEs with important clinical consequences were rare. One apparent difference between the IDE and PAS trials was the greater number of conduit rupture/dissection events reported in PAS than in IDE. On deeper examination of that AE category, which was not specifically defined in either trial, almost all the reports were of contained tears that did not cause any hemodynamic compromise and were often treated with a covered stent or the Melody valve. The analysis did not reveal any obvious difference in practice, such as more aggressive gradient reduction or substantially more use of covered stents, that might explain a higher

incidence of conduit injury in PAS. It has been shown that such limited conduit tears are common consequences of conduit angioplasty (33), and the difference in reports may not have reflected a difference in incidence so much as one of reporting. Either way, all but one of the "ruptures" were inconsequential. Regardless, although the patients enrolled in PAS provided additional prospective data that have contributed to a number of important multi-trial analyses (29,30,32), the PAS trial was not sufficiently powered to facilitate incisive analysis of uncommon outcomes in its own right.

Freedom from stent fracture was significantly shorter among IDE than PAS patients, which follows from the lower frequency of pre-stenting discussed above. Other time-related outcomes in both trials were generally comparable, with a similar incidence of RVOT reintervention overall, although with more surgical valve replacement in PAS and more transcatheter reintervention in the IDE trial. It is unclear if this reflects differences in clinical decision-making, but the greater number of catheter-based reinterventions in the IDE trial was accounted for primarily by valve-in-valve implant for stenosis related to stent fracture, which was more common in the IDE trial and decreased substantially after incorporation of pre-stenting (29). The difference in valve-related endocarditis observed in PAS may also reflect the benefits of prior experience and differences in clinical decision-making, as the overall incidence of any endocarditis was similar, and the criteria for categorizing endocarditis as valve-related was not clearly defined in the protocols. There were only 17 endocarditis cases in either trial, which limits our ability to perform adequate multivariable analysis focused on this outcome. There were relatively few deaths in either trial, and none related to the device or therapy per se, although 3 were due to endocarditis and sepsis. Neither trial separately, nor combined, was powered to provide insight into factors associated with mortality.

Among surviving patients who had not undergone intervention, TPV function and NYHA class were similarly excellent throughout follow-up. As in prior studies, few patients developed moderate (n=8) or severe (n=2) TPV regurgitation, and of the 10 who did, it was during or following an episode of endocarditis in half. Although the similarity between trials supports the observation that PR is uncommon after TPVR with the Melody valve, the small number of affected patients precludes robust estimation of incidence rates or risk factors.

Implications for Post-Approval Evaluation of Class III Medical Devices

The best way to accumulate post-approval safety and efficacy data for class III devices, particularly those used to treat congenital heart disease and other relatively small-market populations, is unclear. While procedural outcomes are obviously important, it is clear that for many devices, including transcatheter valves, some of the most relevant safety and efficacy outcomes manifest over time, such that early surveillance is insufficient. Public reporting of trial results is essential to providing informed consent, but small post-approval studies are of questionable benefit beyond the initial pivotal trial, given the lack of power to identify rare events and discern important associations. While trials such as the Melody valve PAS may shed light on obvious disparities in outcomes in a “real world” environment outside the highly regulated IDE study platform, the small number of patients limits insight into subtle or minor differences. Other approaches, such as mandated registry participation for commercial implants, as with the TVT Registry for transcatheter aortic valve replacement, offer the advantage of larger numbers, but at the cost of incomplete and unverified data. The broader issue of pediatric device development and regulatory approval is complicated, and, approved devices such as the Melody valve notwithstanding, pediatric interventional cardiac procedures frequently employ devices

approved for other applications in an off-label manner (34-37). There is increasing attention to the importance of obtaining formally approved indications for such procedures. However, in a landscape in which costly trials are often prohibitive for devices aimed at the small commercial market of congenital heart disease, it is imperative that we seek to identify economically feasible means of ensuring the safety and clinical appropriateness of devices developed for and currently used in such patients. This study was not designed to answer the question of whether the 100-patient PAS was optimally cost-effective for obtaining useful data to supplement those derived from the IDE trial, but it did show that the results obtained in the IDE trial could be more-or-less replicated in a "real world" environment.

CONCLUSION

Although there were minor differences in patient populations and procedural factors between the Melody valve IDE trial that was used to apply for device approval and the PAS stipulated as a condition of approval, outcomes were generally similar, with several differences that almost certainly fell within the expected range of variation for this therapy. While these studies reflect the experience of early adopter sites in the United States and speak to the American regulatory system, extensive experience gained in other centers and locales is equally important to incorporate into our evolving understanding of this therapy (26-28).

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FIGURE LEGENDS

Figure 1. These Kaplan-Meier (KM) curves depict the estimated freedom from (A) hemodynamic dysfunction, (B) any stent fracture, and (C) major stent fracture at 5 years among patients implanted >24 hours. CI, confidence interval; IDE, Investigational Device Exemption; PAS, Post-Approval Study.

Figure 2. These Kaplan-Meier (KM) curves depict the estimated freedom from (A) any reintervention, (B) catheter-based reintervention, and (C) Melody valve explant at 5 years among patients implanted >24 hours. CI, confidence interval; IDE, Investigational Device Exemption; PAS, Post-Approval Study.

Figure 3. These Kaplan-Meier (KM) curves depict the estimated freedom from (A) any endocarditis and (B) transcatheter pulmonary valve (TPV) endocarditis at 5 years among patients implanted >24 hours. CI, confidence interval; IDE, Investigational Device Exemption; PAS, Post-Approval Study.

Figure 4. These graphs depict hemodynamic and functional status outcomes over time among patients implanted >24 hours. (A) This box plot depicts the right ventricular outflow tract (RVOT) mean gradient over time. Data are site reported. The box is centered at the median, with upper and lower bounds of the box being the 75th and 25th percentiles, respectively. The upper and lower ends of the whiskers are at 1.5 interquartile range (IQR) from the 75th or 25th percentile, respectively, or at the maximum of the observations, whichever is smaller. Circles represent values 1.5 IQR above 75th percentile or 1.5 IQR below 25th percentile. The filled circle is the mean of the observations. (B and C) These column charts summarize (B) the severity of pulmonary regurgitation and (C) the distribution of patients according to New York Heart

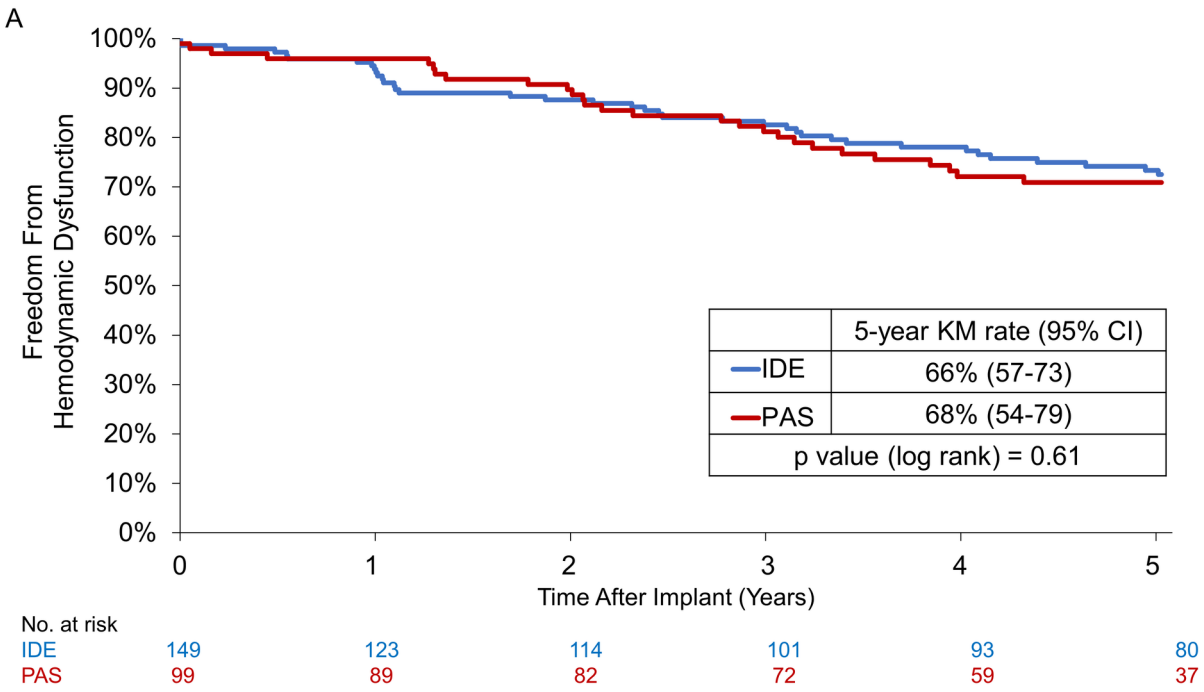
Association (NYHA) class over time. IDE, Investigational Device Exemption; PAS, Post-Approval Study.

SUPPLEMENTARY FIGURE LEGENDS

Supplementary Figure 1. Disposition of patients in the Melody Transcatheter Pulmonary Valve Investigational Device Exemption Trial (A) and Post-Approval Study (B) through 5 years of follow-up. In the Post-Approval Study, 1 patient previously reported as exited prior to catheterization has been reclassified into the catheterized cohort following the last report (which occurred after the 1-year publication[18]).This patient was catheterized but was not implanted with the Melody TPV as the patient was determined to be ineligible based on the echocardiography inclusion criteria.

Supplementary Figure 2. These competing outcome curves demonstrate the cumulative incidences of death (red), any reintervention without death (blue), and survival without reintervention (black) in the Melody Transcatheter Pulmonary Valve Investigational Device Exemption Trial (A) and the Post-Approval Study (B) through 5 years of follow-up. The curves for any reintervention and for death represent the estimated cumulative incidence functions of these events at 5 years. The curve for alive without reintervention is a Kaplan-Meier estimate.

Supplementary Figure 3. Competing risk analysis of the cumulative incidences of death (red), explant without death (blue), and survival without explant (black) in the Melody Transcatheter Pulmonary Valve Investigational Device Exemption Trial (A) and Post-Approval Study (B) through 5 years of follow-up. The curves for explant and for death represent the estimated cumulative incidence functions of these events at 5 years. The curve for alive without reintervention is a Kaplan-Meier estimate.



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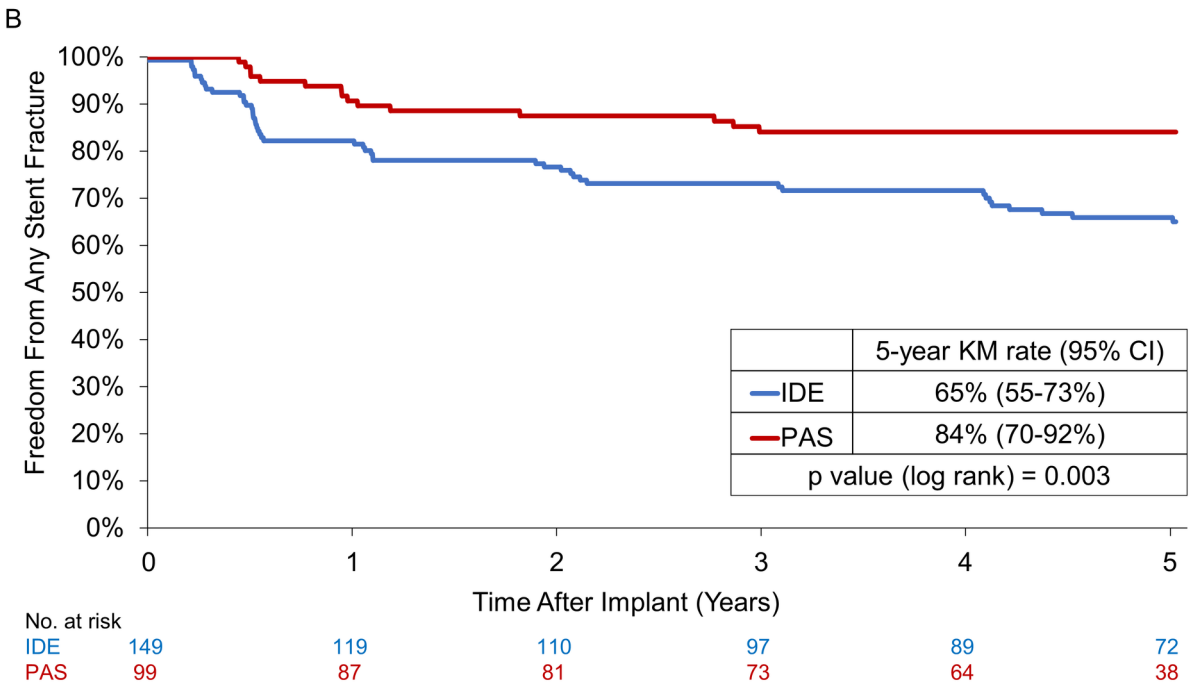

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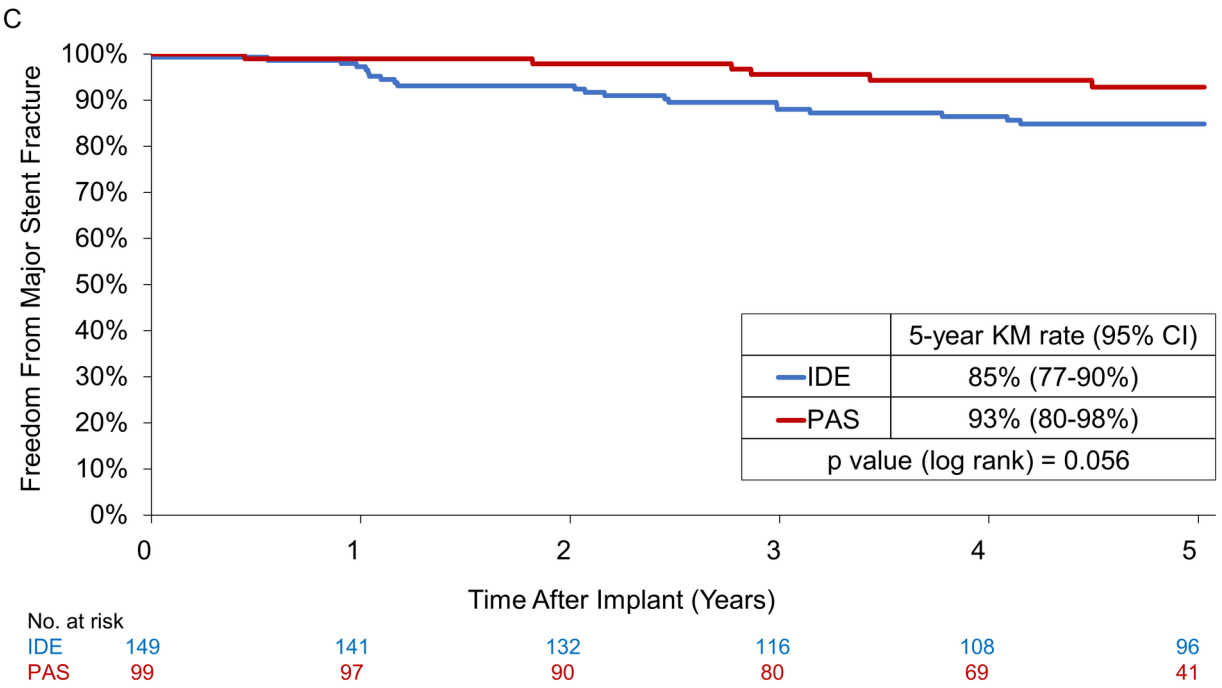

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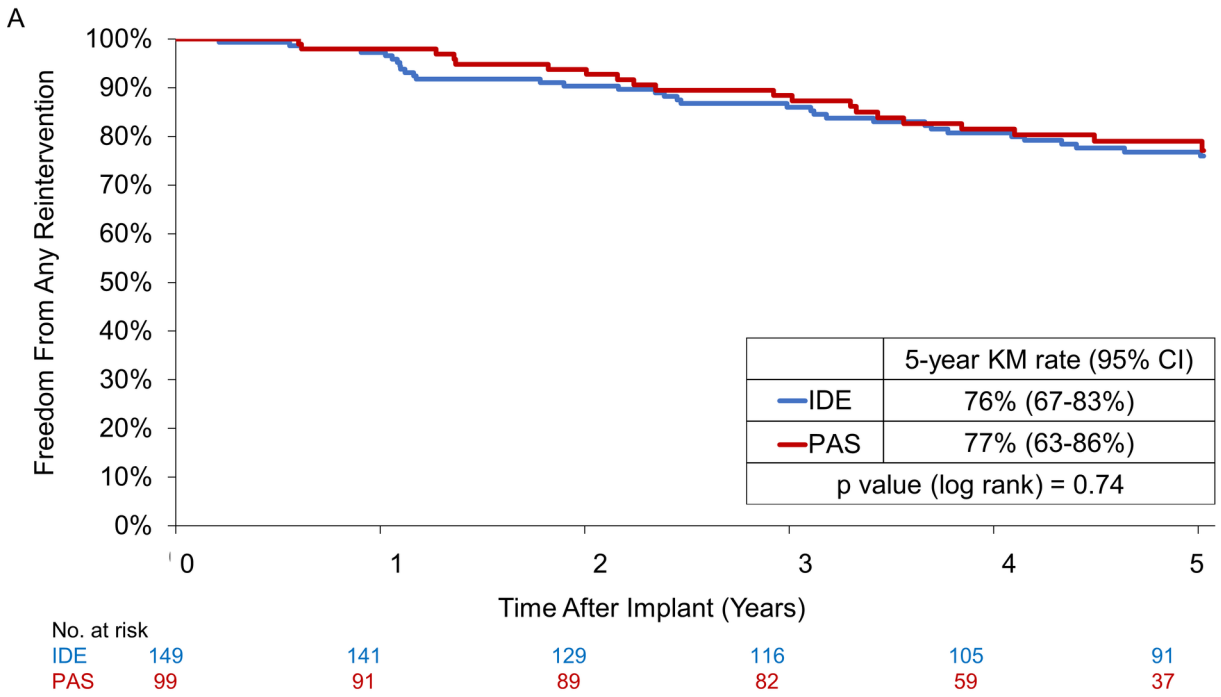

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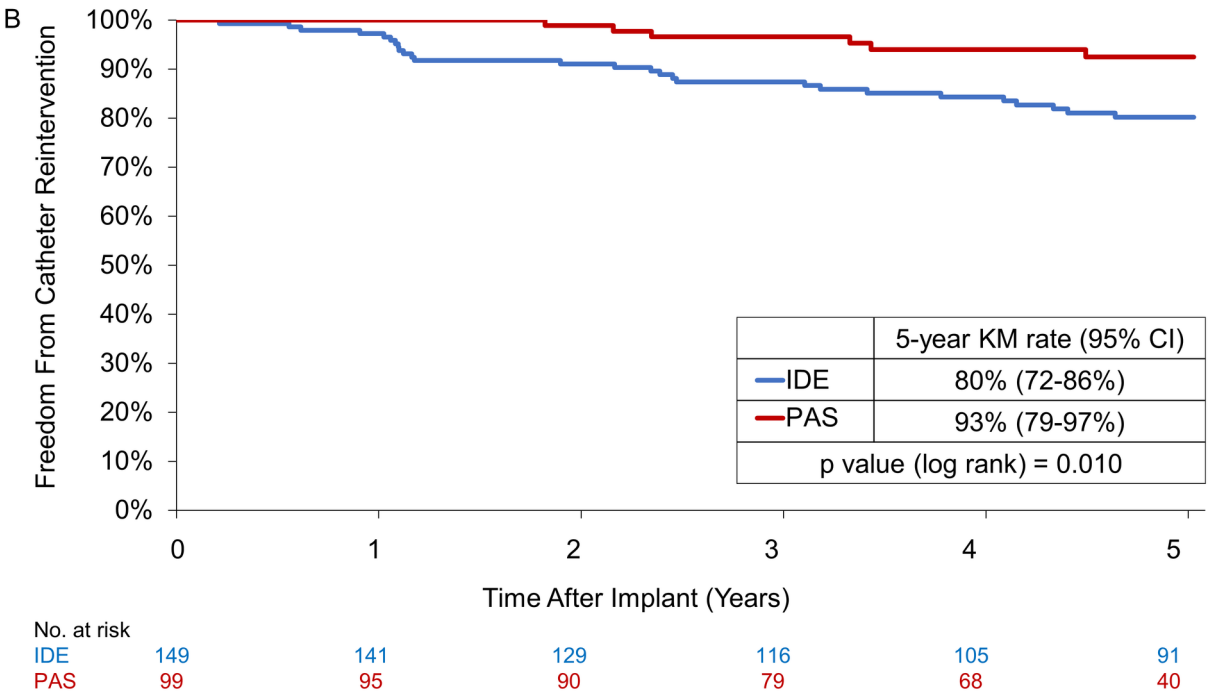

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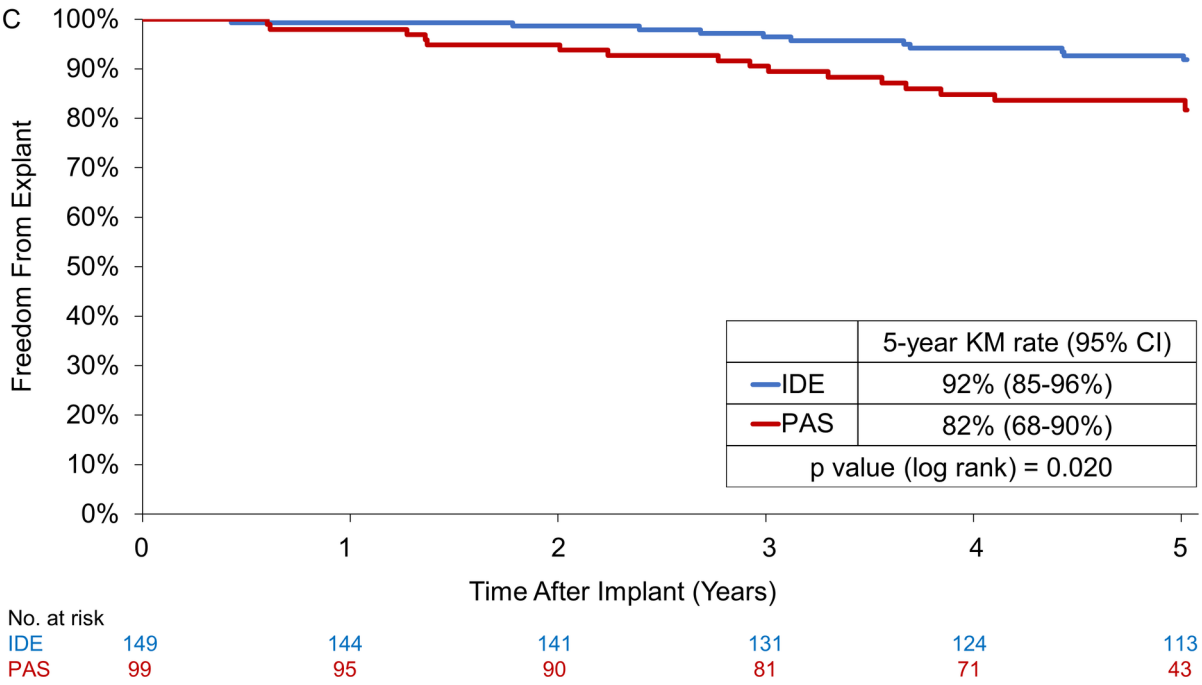

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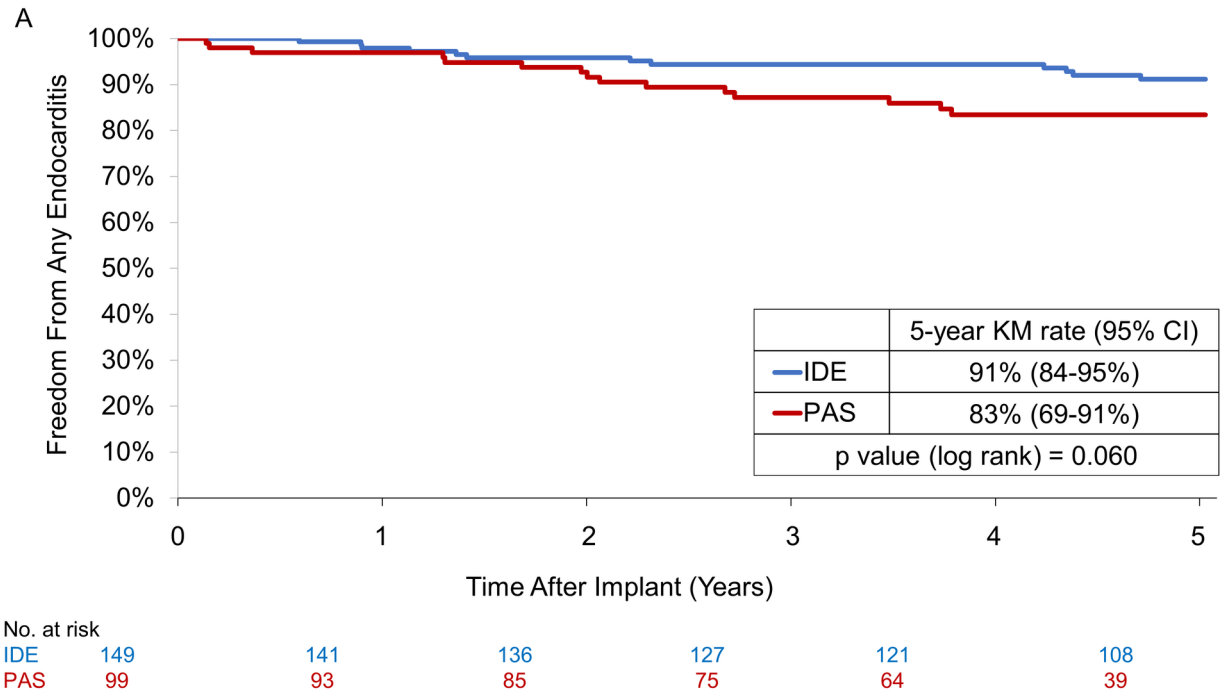

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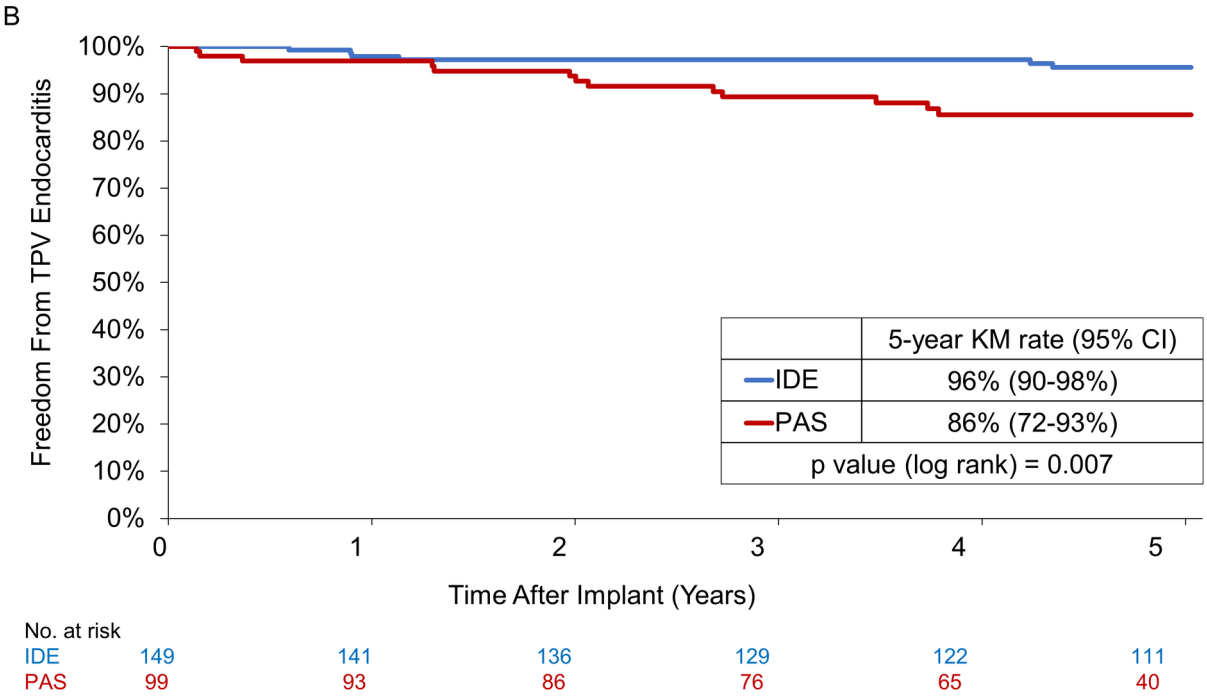

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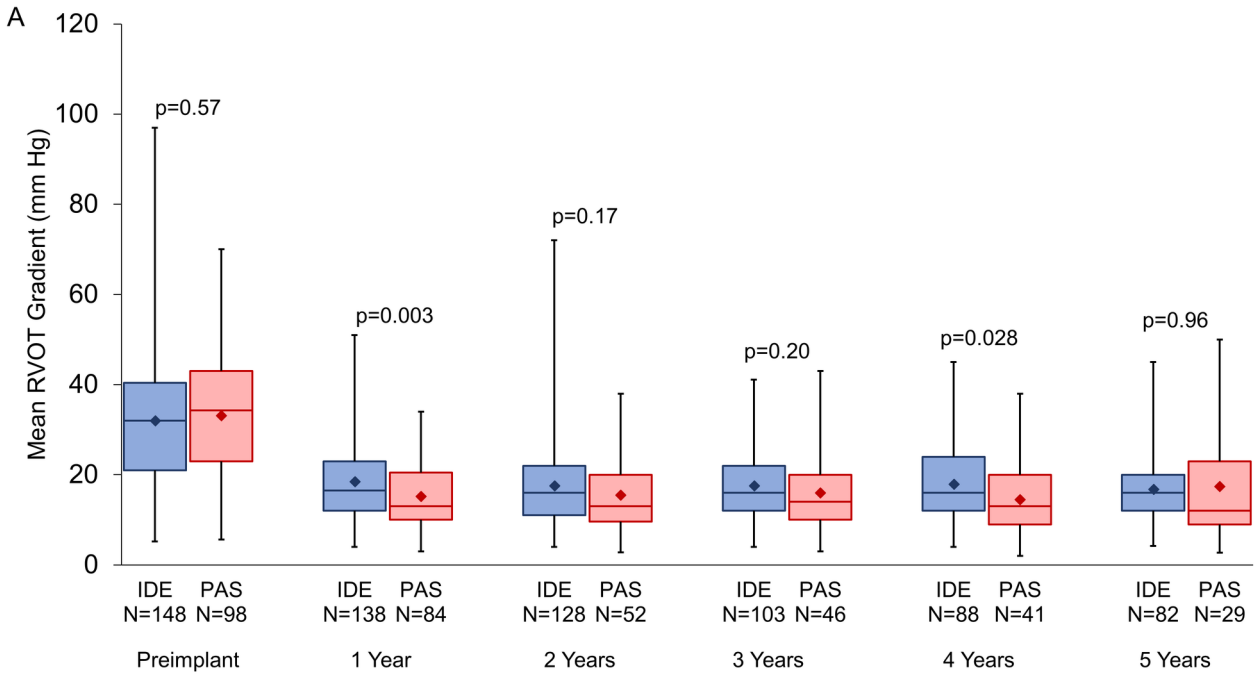
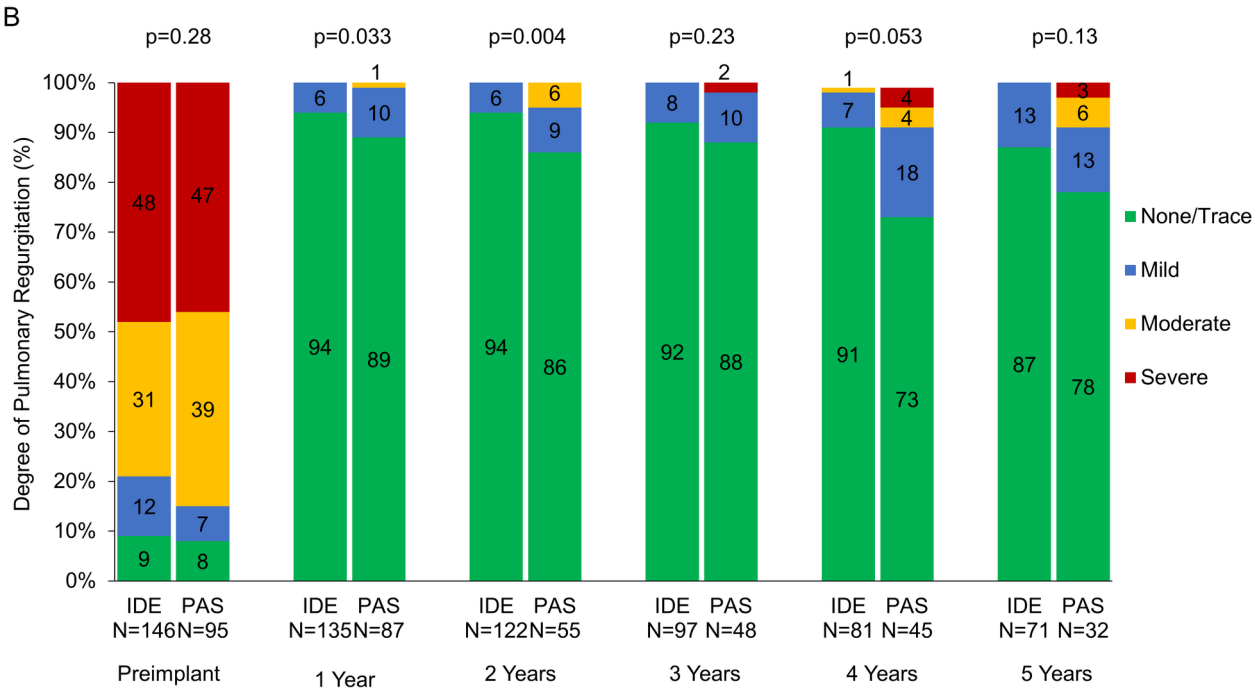


CCD_29657_Fig 4A Melody PAS vs IDE RVOT mean gradient.tif



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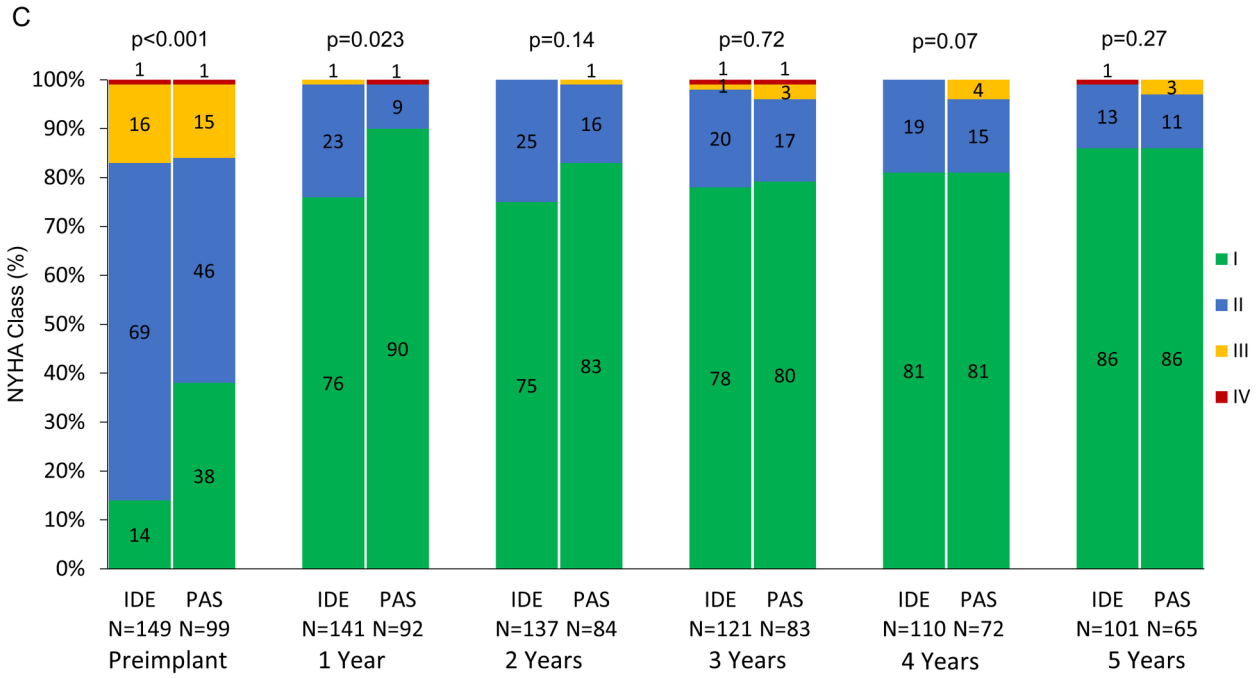

CCD_29657_Fig 4C Melody PAS vs IDE NYHA.tif

Table I. Reasons TPV implant was not attempted in the IDE and PAS trials among patients who underwent catheterization

Reason TPV Implant Not Attempted	**IDE (N=167)**	**PAS* (N=121)**
Coronary artery compression risk	6 (3.59%)	6 (4.96%)
Hemodynamics favorable after balloon dilation/stent only	1 (0.60%)	5 (4.13%)
Hemodynamics favorable - baseline	3 (1.80%)	3 (2.48%)
RVOT anatomy unfavorable - too large	6 (3.59%)	1 (0.83%)
RVOT anatomy unfavorable - unfavorable for other reasons	1 (0.60%)	4 (3.31%)
Need for surgical repair of another heart condition	0 (0%)	1 (0.83%)

IDE, Investigational Device Exemption; PAS, Post-Approval Study; RVOT, right ventricular outflow tract; TPV, transcatheter pulmonary valve. *One patient underwent attempted implant but did not receive a TPV.

Table II. Baseline demographic and diagnostic variables in implanted patients in both trials

Assessment	Implanted Patients		
	IDE (N=150)	**PAS (N=100)**	**p Value IDE vs. PAS**
Weight (kg)	63 (51, 76)	59 (47, 71)	0.20
<30 kg	1 (1%)	6 (6.0%)	0.02
Sex			0.51
Male	96 (64%)	68 (68%)	
Female	54 (36%)	32 (32%)	
Age (years)	19 (15, 26)	17 (13, 25)	0.19
≤12 years	18 (12%)	21 (21%)	
≥22 years	60 (40%)	37 (37%)	
Original diagnosis			0.03
Tetralogy of Fallot	77 (51%)	39 (39%)	
Aortic valve disease (Ross)	31 (21%)	17 (17%)	
Other	42 (28%)	44 (44%)	

No. of prior open-heart surgeries	2 (2, 3)	2 (2, 3)	0.24
NYHA functional class		N=96	<0.001
I	21 (14%)	36 (38%)	
II	104 (69%)	45 (47%)	
III	24 (16%)	14 (15%)	
IV	1 (1%)	1 (1%)	
RVOT conduit/valve type			0.006
Homograft	110 (73%)	65 (65%)	
Biological valved conduit	22 (15%)	14 (14%)	
Bioprosthesis	10 (7%)	17 (17%)	
Synthetic	8 (5%)	1 (1%)	
Other stentless biologic valve	0 (0%)	3 (3.0%)	
Other	0 (0%)	0 (0%)	
RVOT conduit size (mm)	21 (19, 23)	21 (19, 23)	0.70
Bioprosthesis size (mm)	22 (20, 23)	25 (23, 25)	0.02
Pre-existing stent in RVOT conduit			0.19

No pre-existing stents	113 (75%)	85 (85.0%)	
Single stent	24 (16%)	10 (10%)	
Multiple stents	13 (9%)	5 (5%)	
Primary indication for TPVR			0.07
Stenosis	39 (26%)	17 (17%)	
Regurgitation	80 (53%)	51 (51%)	
Mixed	31 (21%)	32 (32%)	
Conduit/valve function*			
PR severity	N=147	N=96	0.29
None	8 (5%)	2 (2%)	
Trace	5 (3%)	6 (6%)	
Mild	18 (12%)	7 (7%)	
Moderate	45 (31%)	37 (39%)	
Severe	71 (48%)	44 (46%)	
Mean RVOT gradient (mmHg)	33 (21, 40)†	34 (23, 43)‡	0.54

Values are n (%) or median (Q1, Q3) unless otherwise noted.

IDE, Investigational Device Exemption; NYHA, New York Heart Association; PAS, Post-Approval Study; PR, pulmonary regurgitation; RVOT, right ventricular outflow tract; TPVR, transcatheter pulmonary valve replacement.

*As determined by site-read echocardiograms for both trials (there was no core laboratory for the PAS trial). †N=148. ‡N=97.

Table III. Procedural data for implanted patients in the IDE and PAS trials

Assessment*	Implanted Patients		
	IDE (N=150)	**PAS (N=100)**	**p Value IDE vs. PAS**
Venous site access			0.01
Femoral vein	143 (95%)	87 (87%)	
Internal jugular vein	6 (4%)	13 (13%)	
Subclavian vein	1 (1%)	0 (0%)	
Concomitant procedures[†]			
No concomitant procedures	84 (56%)	16 (16%)	<0.001
RVOT pre-stent placement, any	54 (36%)	76 (76%)	<0.001
Branch PA stent or angioplasty	13 (9%)	18 (18%)	0.03
Other	9 (6%)	9 (9%)	0.37
Size of delivery system			0.21
18 mm	23 (15%)	8 (8%)	

20 mm	41 (27%)	32 (32%)	
22 mm	86 (57%)	60 (60%)	
Narrowest diameter at intended site of implantation (mm)	13.0 (10.3, 16.0)	13.7 (11.0, 16.0)‡	0.03
Unable to assess/not reported	0 (0%)	9 (9%)	<0.001
Balloon pre-dilation	146 (97%)	85 (85%)	<0.001
Balloon post-dilation	69 (46%)	35 (35%)	0.08
Length of hospital stay (days)	1.0 (1.0, 1.0) (N=149)	1.0 (1.0, 1.0)	0.44
Post-implant peak RV-PA gradient (mmHg)	13.0 (9.0, 17.0)	12.0 (7.0, 17.0)§	0.42
Gradient <15 mmHg	90 (60%)	64 (65%)§	0.46
	10.0 (6.0, 12.0)	8.0 (6.0, 12.0)	
Gradient ≥15 mmHg	60 (40%)	35 (35%)	0.46
	19.0 (16.0, 22.0)	20.0 (16.0, 23.0)	

Values are n (%) or median (Q1, Q3) unless otherwise noted.

IDE, Investigational Device Exemption; PA, pulmonary artery; PAS, Post-Approval Study; RV, right ventricular; RVOT, right ventricular outflow tract.

*Flouroscopy time was not collected in the PAS study. †Patients may have had >1 concomitant procedure. ‡N=91. §N=99.