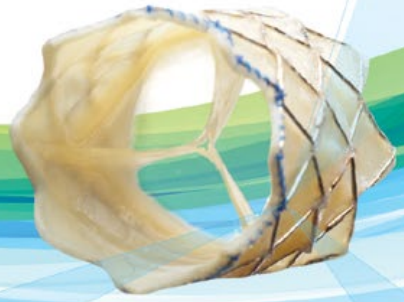
Medtronic

# Melody®

TRANSCATHETER PULMONARY VALVE THERAPY

# Value Summary

## The Clinical and Economic Value of Melody Transcatheter Pulmonary Valve (TPV) Therapy for RVOT Conduit Dysfunction



Proven Performance,
Simply Delivered

# Congenital Heart Disease and RVOT Conduit Dysfunction

## Background & Incidence

Congenital heart disease is a problem with the heart's structure and function that is present at birth in approximately 8 out of every 1000 babies. Of these, 20% have specific heart defects that involve the Right Ventricular Outflow Tract (RVOT) and pulmonary valve which causes blood to flow abnormally between the heart and the lungs. Common forms of RVOT defects include:

- Tetralogy of Fallot
- Pulmonary atresia
- Truncus arteriosus
- Transposition of the great arteries

Children with these complex cardiac anomalies typically undergo surgical repair in the first days or months of life.[1]

## Standard Treatment

Heart defects involving the RVOT are usually addressed with reconstructive surgery that augments the outflow tract as a means to supply blood flow to the lungs. Through open heart surgery, a prosthetic conduit is surgically implanted to connect the right ventricle (RV) with the main pulmonary artery (PA)—this is often referred to as a RV-PA conduit or RVOT conduit.

## Life of the RVOT Conduit

Although placement of RVOT conduits accomplishes the goal of connecting the heart and lungs in a more normal configuration to improve blood flow, it is usually not the final solution for these patients.[1-3] Conduits are subject to progressive degeneration and will become narrowed or the valve within the conduit will begin to leak over time. Conduits can become calcified, or the patient may simply outgrow the conduit. A failing conduit results in one or both of the following hemodynamic problems:

- Pulmonary Valve Stenosis: the narrowing of the conduit opening which limits blood flow from the heart to the lungs
- Pulmonary Valve Regurgitation: the inability of the valve to fully close allowing blood to leak backward into the right ventricle

Nearly all conduits will require replacement

Studies confirm that nearly all conduits will require replacement during the patient's lifetime. As many as 46% of patients studied required reintervention within 10 years,[3-5] and several surgical revisions are typically needed over their lifetime. However, the integrity of the conduit has been shown to be compromised much sooner. In a study of 48 children receiving homograft valves between 1990 and 1995, blinded serial echocardiographic evaluation showed 56% of the valves had failed at just over four years as measured by increased pulmonary regurgitation and stenosis.[6]



## Challenges of Management

As the RVOT conduit ages, physicians must balance the risks of ongoing conduit dysfunction against the risks and benefits of open heart surgery to replace the conduit.

Open heart surgeries are highly invasive

Multiple open heart surgeries to replace failing RVOT conduits, while effective, are highly invasive and come with substantial risk to the patient.[2,7]

- Procedural complications include mortality, cardiac injury, infection, bleeding requiring reoperation, multiple transfusions, and need for post-operative ventilation.[8,9]
- Reported mortality rate of repeated conduit surgery is 1.7% to 4.9%.[10]
- Cardiopulmonary bypass is required during surgery and has been shown to carry significant complications including:[8,11]
  - Stroke
  - Pneumonia
  - Respiratory failure
  - Need for re-intubation
- Postoperative pain, discomfort and associated impaired quality of life contribute to the burden that open heart surgery patients face.[12]

RVOT conduit dysfunction is generally tolerated for some time however, if left untreated in the longer term, can have detrimental effects on the right and left ventricle functions and has been shown to result in:[7,13-15]

- Reduced exercise tolerance
- Ventricular arrhythmias
- Increased risk of sudden death

Until recently, the management strategy for these patients has been to accept significantly abnormal hemodynamics, often for many years, delaying the need for additional surgery as long as possible.[10]

# Melody® Transcatheter Pulmonary Valve

The Melody Transcatheter Pulmonary Valve (TPV) treats pulmonary valve stenosis and regurgitation without open heart surgery. The TPV is intended to restore RVOT conduit valve function while delaying the patient's next open heart surgery. A minimally invasive procedure is used to deploy the Melody valve within an existing but dysfunctional RVOT conduit. Using a catheter (thin hollow tube), the new valve is inserted into the body through the venous system and then guided to the heart where it is deployed.

Transcatheter pulmonary valve replacement with the Melody valve has been proven safe and effective for patients with post-operative right ventricular outflow tract (RVOT) conduit dysfunction.

The Melody TPV has been proven to:

- Relieve conduit obstruction
- Restore valve function
- Delay the patient's next surgical conduit replacement

## A Less Invasive Approach to Restore Valve Function

# Melody TPV is Proven Safe and Effective

Melody TPV has been studied by Medtronic since 2007. The accumulated data from the following three studies present 313 subjects implanted with the valve. These data provide a large body of consistently excellent clinical results demonstrating the safety and effectiveness of the Melody TPV and Ensemble Delivery System in the following studies:

**US IDE Study[16,17]**
Prospective, non-randomized investigational study conducted at 5 centers. 150 subjects implanted between January 2007 and January 2010; patients will be followed for 10 years. Data presented is interim results current through March 1, 2014 (mean length of follow-up 4.4 ± 1.3 years).

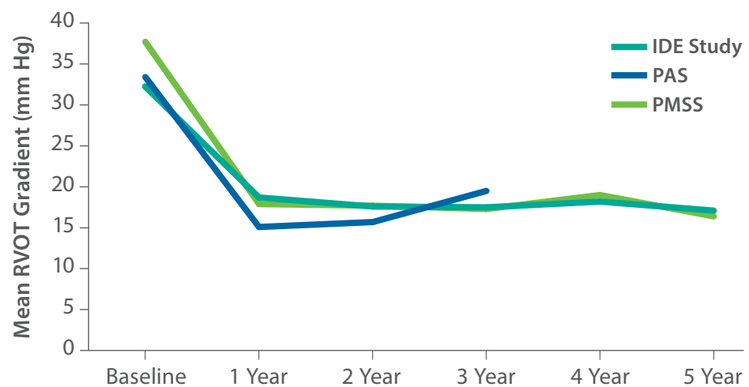
**US Post Approval Study (PAS)[18]**
Prospective, non-randomized study conducted at 10 centers. 100 subjects implanted between July 2010 and July 2012; patients will be followed for 5 years. Data presented is interim results through March 1, 2014 (mean length of follow-up 2.1 ± 0.8 years).

**European and Canadian Post-Market Surveillance Study (PMSS)**
Prospective, non-randomized study conducted at 7 centers in Europe and Canada. 63 subjects implanted between October 2007 and April 2009; patients will be followed for 5 years. Data presented is interim results through March 1, 2014 (mean length of follow-up 4.2 ± 1.1 years).

## Improvements in RVOT Gradient

Studies demonstrate mean RVOT gradient decreases and remains consistent throughout follow-up to five years.[19]

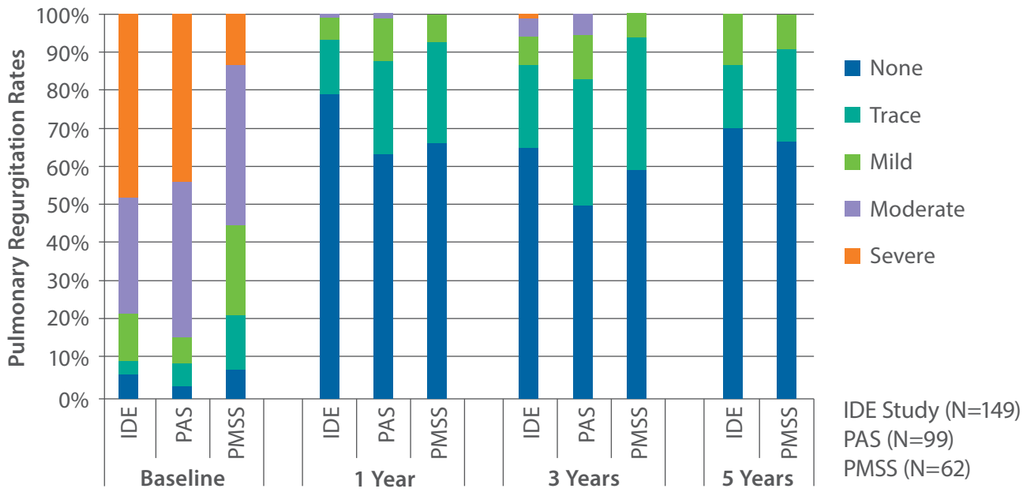
| Mean RVOT Gradient By Time Interval | Baseline | 1 Year | 3 Year | 5 Year |
|---|---|---|---|---|
| IDE Study (N=149) | 32.1 ± 13.9 | 18.7 ± 9.1 | 17.5 ± 7.8 | 17.1 ± 7.5 |
| Post-Approval Study (N=99) | 33.4 ± 14.1 | 15.1 ± 7.1 | 19.5 ± 15.4 | -- |
| Post-Market Surveillance Study (N=62) | 37.7 ± 12.1 | 17.9 ± 9.2 | 17.3 ± 8.4 | 16.4 ± 8.6 |



# Melody TPV is Proven Safe and Effective

## Improvements in Pulmonary Valve Regurgitation

Patients with moderate to severe pulmonary valve regurgitation at baseline demonstrated significant and sustained improvement throughout follow-up to five years.[19]




## Low Rates of Device-Related Adverse Events

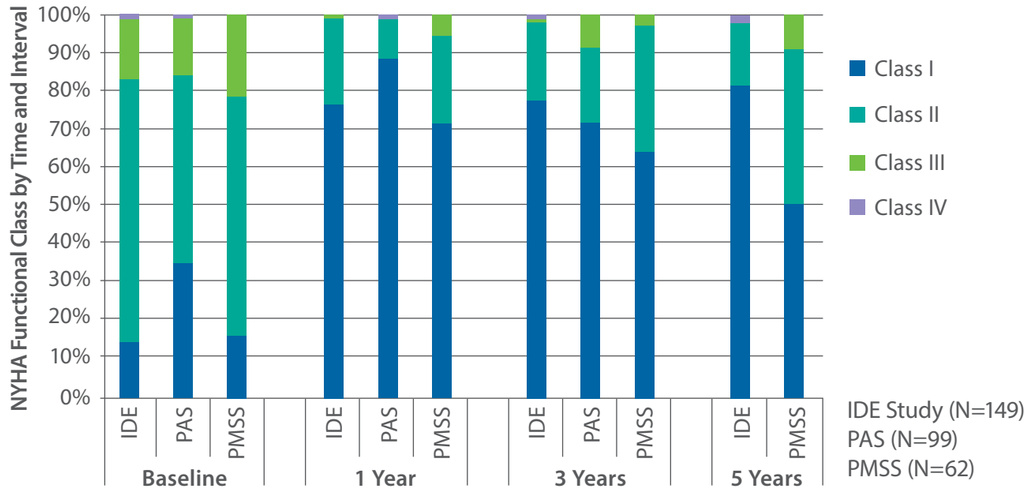
Studies demonstrate low rates of serious device-related adverse events across all categories throughout follow-up to five years.[19]

| | IDE Study | PMSS | PAS |
|---|---|---|---|
| Event | Freedom from event at 5 years (SE) (N=149) | Freedom from event at 4 years (SE) (N=62) | Freedom from event at 2 years (SE) (N=99) |
| Stent Fracture: Major | 84.3% (4.5%) | 91.5% (3.8%) | 97.6% (1.9%) |
| Valve Dysfunction: Stenosis | 79.9% (4.9%) | 86.1% (4.7%) | 96.3% (2.3%) |
| Valve Dysfunction: Regurgitation | 99.2% (1.1%) | 98.3% (1.8%) | 96.7% (2.3%) |
| Prosthetic Valve Endocarditis | 96.1% (2.4%) | 94.9% (3.0%) | 92.9% (3.2%) |
| Embolization of the TPV | 100.0% (-) | 100% (-) | 100.0% (-) |



## Improvements in Quality of Life

Improvements were demonstrated in NYHA class designation following Melody TPV implant which remained consistent during follow-up.[19]




## Additional Studies Illustrate Improvements in Quality of Life

A prospective, single-center study of 59 patients (46 with mainly pulmonary stenosis and 13 with mainly pulmonary regurgitation) treated with Melody TPV between July 2007 and March 2013 showed significant improvements 6 months after intervention. Using the medical outcome study 36 short form (SF-36), self-estimated improvements were measured in:[20]

- Physical function
- General health perception
- Health transition
- Physical role functioning
- Vitality
- Mental health

While significant improvements in quality of life were seen in all 59 patients, the patients with pulmonary stenosis (46) showed significant improves in the above measures.

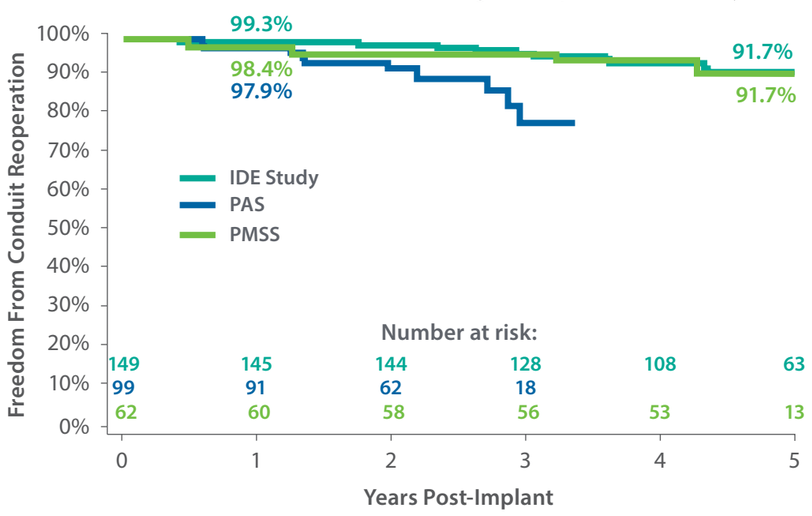
# Melody TPV is Proven Safe and Effective

## Delays the Need for Open Heart Surgery

Multiple studies confirm Melody TPV placement delays the need for open heart surgery indicating the potential for reducing the number of open heart surgeries in patients with RVOT conduit dysfunction over a lifetime.[21,22]

- A study by Lurz et al. published in 2008 showed freedom from reoperation for patients receiving Melody TPV between September 2000 and February 2007 (n=150):[21]
  - 93% (±2%) at 10 months
  - 86% (±3%) at 30 months
  - 84% (±4%) at 50 months
  - 70% (±13%) at 70 months
- A study by Vezmar et al. published in 2010 showed freedom from reoperation for patients receiving Melody TPV between October 2005 and December 2008 (n=28):[22]
  - 91% at 12 months
  - 83% at 24 months
  - 83% at 36 months

Medtronic studies demonstrate low rates of surgical reoperation out to 5 years[19]






# Melody TPV is Economically Advantageous

## Two Analyses Demonstrate Melody TPV Provides Value Compared to Surgical Revision

A US cost analysis by Vergales, et al., published in 2013, used a decision-tree approach with Markov modeling, to compare a five-and 10-year cost model for both TPV implantation (n=17) and surgical revision (n=17). The analysis showed significant cost advantages for TPV:[23]

- Average length of stay (p <0.001)
  - TPV = 1 day
  - Surgical revision = 5.7 days
- Average procedural charges (p <0.001)
  - TPV = $80,327
  - Surgical revision = $126,406
- Average wage loss for patient/caregiver (p <0.001)*
  - TPV = $611
  - Surgical revision = $3,113
- Projected costs at 5 years**
  - TPV = $106,276
  - Surgical revision = $141,273
- Projected costs at 10 years**
  - TPV = $121,482
  - Surgical revision = $150,438

* Calculated as the product of the patient's average daily wage and lost days of work (patient's length of stay + recommended time away).
** Cost projections are based on hospital and procedure charges billed to the payer July 2010 through September 2011. Five (5) and ten (10) year cost projections are based on a decision tree computer model using TreeAge Pro Healthcare version 2012 (TreeAge Software, Williamstown, MA).

A UK cost simulation model published in 2011 by Raikou, et al. used a cohort simulation applied to a hypothetical population of 1,000 individuals with RVOT dysfunction over a 25 year period, compared two assumptions: the first being the absence of TPV technology and the second the availability of TPV technology. Management costs calculated reflect early experience with the procedure which have evolved over the years. Even so, for the benefit of a less invasive treatment option that helps patients avoid the risks of surgery for a longer period, the analysis showed TPV was associated with only a relatively small increase in treatment management cost:[15]

- Mean cost per patient
  - TPV available = £8,734 ($12,796)†
  - TPV unavailable = £5,791 ($8,483)†
- Cost of within-year complications
  - TPV = £348 ($510)†
  - Surgical revision = £1,501 ($2,199)†

† British pounds converted to USD using Reuters currency converter on 4/10/15.

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## Melody® Transcatheter Pulmonary Valve, Ensemble® Transcatheter Valve Delivery System

Important Labeling Information for United States.

**Indications:** The Melody TPV is indicated for use as an adjunct to surgery in the management of pediatric and adult patients with the following clinical conditions:

- Existence of a full (circumferential) RVOT conduit that was equal to or greater than 16 mm in diameter when originally implanted AND
- Dysfunctional RVOT conduits with a clinical indication for intervention, AND:
  -regurgitation: ≥ moderate regurgitation, AND/OR
  -stenosis: mean RVOT gradient ≥ 35 mm Hg

**Contraindications:** None known.

Warnings/Precautions/Side Effects:

- **DO NOT implant in the aortic or mitral position. Preclinical bench testing of the Melody valve suggests that valve function and durability will be extremely limited when used in these locations.**
- DO NOT use if patient's anatomy precludes introduction of the valve, if the venous anatomy cannot accommodate a 22-Fr size introducer, or if there is significant obstruction of the central veins.
- DO NOT use if there are clinical or biological signs of infection including active endocarditis. Standard medical and surgical care should be strongly considered in these circumstances.
- Assessment of the coronary artery anatomy for the risk of coronary artery compression should be performed in all patients prior to deployment of the TPV.
- To minimize the risk of conduit rupture, do not use a balloon with a diameter greater than 110% of the nominal diameter (original implant size) of the conduit for pre-dilation of the intended site of deployment, or for deployment of the TPV.
- The potential for stent fracture should be considered in all patients who undergo TPV placement. Radiographic assessment of the stent with chest radiography or fluoroscopy should be included in the routine postoperative evaluation of patients who receive a TPV.
- If a stent fracture is detected, continued monitoring of the stent should be performed in conjunction with clinically appropriate hemodynamic assessment. In patients with stent fracture and significant associated RVOT obstruction or regurgitation, reintervention should be considered in accordance with usual clinical practice.

Potential procedural complications that may result from implantation of the Melody device include the following: rupture of the RVOT conduit, compression of a coronary artery, perforation of a major blood vessel, embolization or migration of the device, perforation of a heart chamber, arrhythmias, allergic reaction to contrast media, cerebrovascular events (TIA, CVA), infection/sepsis, fever, hematoma, radiation-induced erythema, blistering, or peeling of skin, pain, swelling, or bruising at the catheterization site.

Potential device-related adverse events that may occur following device implantation include the following: stent fracture,* stent fracture resulting in recurrent obstruction, endocarditis, embolization or migration of the device, valvular dysfunction (stenosis or regurgitation), paravalvular leak, valvular thrombosis, pulmonary thromboembolism, hemolysis.

* The term "stent fracture" refers to the fracturing of the Melody TPV. However, in subjects with multiple stents in the RVOT it is difficult to definitively attribute stent fractures to the Melody frame versus another stent.

For additional information, please refer to the Instructions For Use provided with the product.

**CAUTION:** Federal law (USA) restricts this device to sale by or on the order of a physician.

Important Labeling Information for Geographies Outside of the United States

**Indications:** The Melody® Transcatheter Pulmonary Valve is indicated for use in patients with the following clinical conditions:

- Patients with regurgitant prosthetic Right Ventricular Outflow Tract (RVOT) conduits with a clinical indication for invasive or surgical intervention, OR
- Patients with stenotic prosthetic RVOT conduits where the risk of worsening regurgitation is a relative contraindication to balloon dilatation or stenting.
- Existence of a full (circumferential) RVOT conduit that was equal to or greater than 16 mm in diameter when originally implanted.

The intended lifetime for the Melody® device is 2 years.

Contraindications:

- Venous anatomy unable to accommodate a 22 Fr size introducer sheath; Implantation in left heart;
- Unfavorable right ventricular outflow tract for good stent anchorage;
- Severe right ventricular outflow obstruction, which cannot be dilated by balloon;
- Obstruction of the central veins;
- Clinical or biological signs of infection;
- Active endocarditis;
- Known allergy to aspirin or heparin;
- Pregnancy.

**Potential Complications / Adverse Events:** Potential procedural complications that may result from implantation of the Melody device include the following: rupture of the RVOT conduit, compression of a coronary artery, perforation of a major blood vessel, embolization or migration of the device, perforation of a heart chamber, arrhythmias, allergic reaction to contrast media, cerebrovascular events (TIA, CVA), infection/sepsis, fever, hematoma, radiation-induced erythema, pain at the catheterization site.

Potential device-related adverse events that may occur following device implantation include the following: stent fracture resulting in recurrent obstruction, endocarditis, embolization or migration of the device, valvular dysfunction (stenosis or regurgitation), paravalvular leak, valvular thrombosis, pulmonary thromboembolism, hemolysis.

For additional information, please refer to the Instructions For Use provided with the product.

The Melody® Transcatheter Pulmonary Valve and Ensemble® Transcatheter Delivery System has received CE Mark approval and is available for distribution in Europe. Additionally, a Medical Device Licence has been granted and the system is available for distribution in Canada.

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