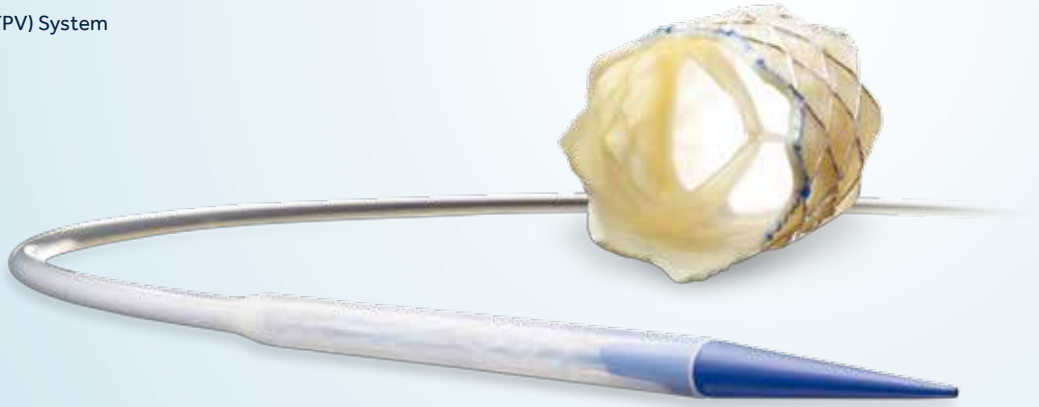
EXPERIENCE MATTERS.

Melody™
Transcatheter Pulmonary Valve (TPV) System



Medtronic
Further, Together

3
prospective clinical trials[1,2]

22
centers[1,2]

309
implanted patients
(The largest prospectively followed TPV cohort)[2]

EXPERIENCE MATTERS

The Melody™ Transcatheter Pulmonary Valve (TPV) was the first transcatheter valve commercially approved. Since 2006, it has benefited over 14,000 patients globally.

MELODY TPV IS TIME-TESTED AND UNSURPASSED IN CLINICAL INVESTIGATION:

- Longest clinical evaluation of any TPV
- Most studied TPV, with several multicenter, prospective clinical trials
- Largest body of TPV clinical evidence

1,660+
patient-years of observation[2] (The longest unprecedented, prospective, post-TPV replacement evaluation)

5+
years median follow-up per patient[2]

7.5+
times more follow-up than Edwards SAPIEN™* Pulmonic THV[2,3]

UNMATCHED CLINICAL EVIDENCE

Compiled data from Melody TPV trials provide a large body of consistently excellent clinical results demonstrating safety and effectiveness of the Melody TPV and Ensemble™ Delivery systems. These data have demonstrated:

- Delayed next surgical conduit or bioprosthetic valve (BPV) replacement[4,5]
- Delayed need for open-heart surgery[4,5]
- Low rates of surgical reoperation[4]
- Low rates of device-related serious adverse events[1]
- Improvements in Right Ventricular Outflow Tract (RVOT) gradients[1]
- Improvements in quality of life[1,6]

Melody TPV Prospective, Multicenter Clinical Trials[1]

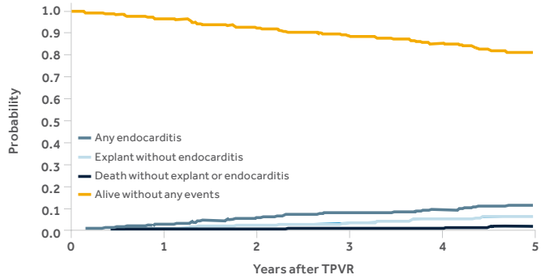
Study	# of Centers	# of Patients	First Study Implant	Last Study Implant	Mean Length of Follow-up
U.S. IDE	5	150	2007	2010	6.5 ± 2.0 years
U.S. PAS	10	100	2010	2012	4.1 ± 1.2 years
EU/CA PMSS	7	63	2007	2009	4.7 ± 1.1 years

U.S. Investigational Device Exemption Study (IDE) | U.S. Post-approval Study (PAS) | EU/CA Post-market Surveillance Study (PMSS)

Medtronic-sponsored Studies: What Does the Data Show?[2]

Medtronic Melody TPV	Total Patient Years of Follow-up
3 prospective, long-term clinical trials: ▪ U.S. Investigational Device Exemption Study (IDE) ▪ Melody TPV U.S. Post-approval Study (PAS) ▪ Melody TPV EU/CA Post-market Surveillance Study (PMSS)	**1,660.3**

Low Cumulative Incidences of Adverse Events at 5 Years Post-Melody™ TPV implant[2]



Sources: Melody TPV U.S. Investigational Device Exemption Study (IDE); Melody TPV U.S. Post-approval Study (PAS); Melody TPV EU/CA Post-market Surveillance Study (PMSS). (N = 309).[2]

Low Incidence of Adverse Events

at 5 Years Post-Melody TPV Implant[2]:

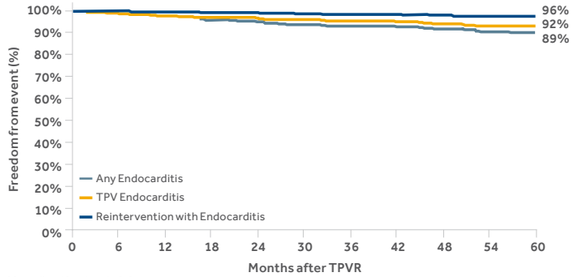
2.4%
Annualized incidence of TPV infective endocarditis[2]

82%
Patients without major adverse events[2]

89.3%
Freedom from explant at 5 years[2]

48%
Of those patients who developed endocarditis were medically managed without reintervention[2]

Melody TPV Kaplan-Meier Freedom from All Endocarditis Events[2]

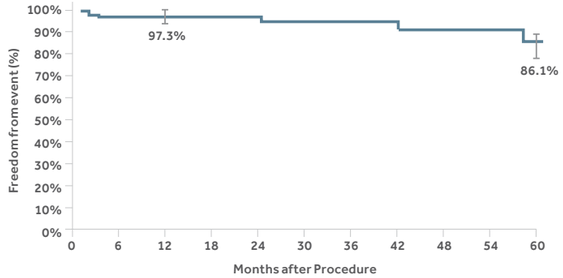


No. of patients at risk

309	296	280	264	245	177
309	296	284	267	247	180
309	302	293	276	256	187

Sources: Melody TPV U.S. Investigational Device Exemption Study (IDE); Melody TPV U.S. Post-approval Study (PAS); Melody TPV EU/CA Post-market Surveillance Study (PMSS). (N = 309)[2]

Edwards SAPIEN™* Pulmonic THV Kaplan-Meier Freedom from THV Endocarditis Events[3]



No. of patients at risk

79	69	61	52	49	44	43	36	23	20	10

Source: Edwards SAPIEN U.S. IFU 2015. COMPASSION Trial. Safety Population (N = 79).[3]

NOTES:
- The two Kaplan-Meier charts above are not intended to be a comparison of the two transcatheter pulmonary valve replacement devices, as there is no head-to-head clinical study comparing the two valves. Rather, these charts are intended to illustrate the clinical results of similar trials.
- Reported rates of freedom from IE are similar based on Kapan-Meier analysis. Multiple factors contribute to clinical study outcomes and need to be considered in making any assessments across different studies.

Freedom from Endocarditis

At 5 years post-pulmonic valve replacement with Melody TPV[2]:

96%
Freedom from reintervention with endocarditis

92%
Freedom from TPV-related endocarditis

89%
Freedom from a diagnosis of any endocarditis

CHALLENGES OF CHD MANAGEMENT

As the RVOT conduit or BPV ages, physicians must balance the risks of ongoing dysfunction against the risks and benefits of open-heart surgery to replace the conduit or surgical valve. RVOT conduit or surgical valve dysfunction is generally tolerated for some time; however, if left untreated in the longer term, it can have detrimental effects on the right and left ventricle functions.[7-10]

The consequences of conduit or valve dysfunction include:

- RV obstruction leading to RV hypertension (pressure overload) is deleterious[11]
- RV volume overload, which is also deleterious[12]
  - Progressive RV dilation and eventual failure
  - Enlarged RV promotes arrhythmogenicity
  - RV dysfunction ultimately leads to LV dysfunction
  - RV failure leads to early mortality

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.[13]

Timely intervention can save RV function and regress dilatation. Multiple open-heart surgeries to replace failing RVOT conduits or surgical valves, while effective, are highly invasive and come with substantial risk to the patient.[7,14]

The Melody TPV treats pulmonary valve stenosis and regurgitation without open-heart surgery. The minimally invasive TPV procedure is intended to restore RVOT conduit or surgical valve function while delaying the patient's next surgical intervention.

INFECTIVE ENDOCARDITIS (IE) RISK IN ALL CONGENITAL HEART DISEASE (CHD) PATIENTS

- 12% of patients with CHD who are indicated for surgical valve replacement have a history of endocarditis prior to valve replacement.[15]
- IE is a potential late complication associated with all types of bioprosthetic valve implants (surgical, RV-PA conduits, transcatheter).
- Healthcare providers are advised that endocarditis risk is one of several factors to consider when pursuing valve replacement options.[2]
- Relative increased incidence as patients with CHD are living longer[16]
- Male gender has been observed as a risk factor of endocarditis.[17]
- Risk of IE might not be intrinsic to valve type, but more related to the environment in which valves are implanted (e.g., RVOT conduits are a risk factor for IE).[18]
- Endocarditis seems to be less common after TPV replacement into a native/patched RVOT.[2]

MELODY™ TPV PROCTOR RECOMMENDATIONS† TO MINIMIZE ENDOCARDITIS RISK

Pre-implant TPV

- Evaluate prior history of endocarditis, if any
- Evaluate cutaneous infections or other systemic infection
- Evaluate all potential sources (skin, teeth and gums, ear, nose, throat)
- Educate patients on lifestyle risk factors:
  - Personal hygiene
  - Nail biting
  - Piercing/tattoos
  - IV drug abuse
  - Chronic skin infection and/or scratch lesions (skin disease, animal or bug bite scratches)
- Successfully treat infections and complete dental work prior to implant
- Educate patients on possible increased risk factors:
  - Congenital heart disease
  - History of endocarditis
  - Comorbidities
  - Complex RVOT
  - Male gender

Post-implant TPV

- Educate patients, parents/guardians, referring physicians, and dentists on risks of endocarditis with implantation of bioprosthetic valve, and on early signs and symptoms of endocarditis:
  - Best dental care post-PPVI
  - Infection in skin lesions (e.g., acne, bug bites, ingrown toenails) should be avoided, if at all possible. If infections develop, they should be treated as quickly as possible, following current guidelines.[19]
  - Lifelong antibiotic prophylaxis prior to any dental and invasive medical procedures
- Prompt and aggressive evaluation of fever
- High index of suspicion for endocarditis
- Clinicians should maintain a high level of concern about endocarditis with Staphylococcus aureus, which was most often associated with severe clinical presentation and mortality.[2]
- Currently, there is no consensus on aspirin protocol (various protocols in use: from none given, to 6-month regimen, to lifelong). Animal studies suggest antiplatelet or anticoagulation therapy may reduce endocarditis risk.**

†This information is provided as an educational resource based on an identified need, but is not intended to constitute medical advice or in any way replace the independent medical judgment of a trained and licensed physician with respect to any patient needs or circumstances. The physician is solely responsible for all decisions and medical judgments relating to the treatment of their patients. Factors, treatment, use, risks, and outcomes may vary. Please see the complete Instructions for Use for products discussed, including all product indications, contraindications, precautions, warnings, and adverse events.

**These tests may not be indicative of clinical performance and are for illustrative purposes only.

CLASSIFYING ENDOCARDITIS

Many leading clinicians who manage CHD patients have found current systems for classifying endocarditis in patients with repaired right-sided CHD inadequate to assess the clinical severity and major outcomes of endocarditis after TPV replacement.[2]

The following proposed clinical classification system and treatment algorithms† are based on Melody™ TPV proctor recommendations that may assist clinicians in developing standard assessment and management tools to facilitate deeper insights into risk for endocarditis in this population.[2]

PROPOSED CLINICAL CLASSIFICATION SYSTEM FOR ENDOCARDITIS AFTER TRANSCATHETER PULMONARY VALVE REPLACEMENT[2]

	TPV Involvement/ Response to Antibiotics	A	B	C
Clinical Severity Category		Definite TPV Involvement	No Evidence of TPV Involvement with Good Noninvasive Imaging	TPV Involvement Cannot Be Determined Definitively with Noninvasive Evaluation
1	**Not Severe** Symptomatic improvement with antibiotics	▪ Follow without acute intervention ▪ Evaluate TPV involvement and need for TPV intervention after full course of antibiotics	▪ Follow without acute intervention ▪ No TPV intervention unless evolution to different clinical category	▪ Follow without acute intervention or invasive evaluation ▪ Otherwise, no invasive evaluation of TPV unless evolution to different clinical category
2	**Intermediate** Not severe but persistent/ recurrent symptoms on antibiotics	▪ Surgical TPV intervention	▪ Consider further evaluation of TPV involvement with catheterization and ICE, or PET ▪ Surgical intervention if ICE/PET positive ▪ Consider surgical intervention if ICE/PET negative	▪ Further evaluation of TPV involvement with catheterization and ICE ▪ Consider acute transcatheter TPV intervention if ICE demonstrates TPV involvement ▪ If catheterization/ICE negative, consider PET to further assess RVOT involvement ▪ Surgical intervention if ICE/PET positive
3	**Severe** Sepsis, shock, end-organ dysfunction, RV dysfunction, severe RVOT obstruction	▪ ECMO if indicated ▪ Acute TPV intervention ▪ Consider temporizing with transcatheter intervention, or ▪ Acute surgical intervention	▪ ECMO if indicated ▪ Supportive medical therapy ▪ Consider further evaluation of TPV involvement with catheterization and ICE, or PET ▪ No acute TPV intervention unless invasive evaluation demonstrates evolution of RVOT obstruction or new TPV involvement	▪ ECMO if indicated ▪ Supportive medical therapy ▪ Further evaluation of TPV involvement with catheterization and ICE ▪ Consider acute transcatheter TPV intervention if ICE demonstrates TPV involvement ▪ If catheterization/ICE negative, consider PET to further assess ▪ Surgical intervention if PET/ICE positive RVOT involvement

▪ Antibiotic therapy is standard for all categories.
▪ In all categories except 1B, evidence of pulmonary embolic complications should be considered an indication for surgical intervention regardless of indeterminate or conflicting evidence about TPV or other intracardiac involvement.

Terms:
ECMO = Extracorporeal membrane oxygenation
ICE = Intracardiac echocardiography
PET = Positron emission tomography
RV = Right ventricle
RVOT = Right ventricular outflow tract
TPV = Transcatheter pulmonary valve

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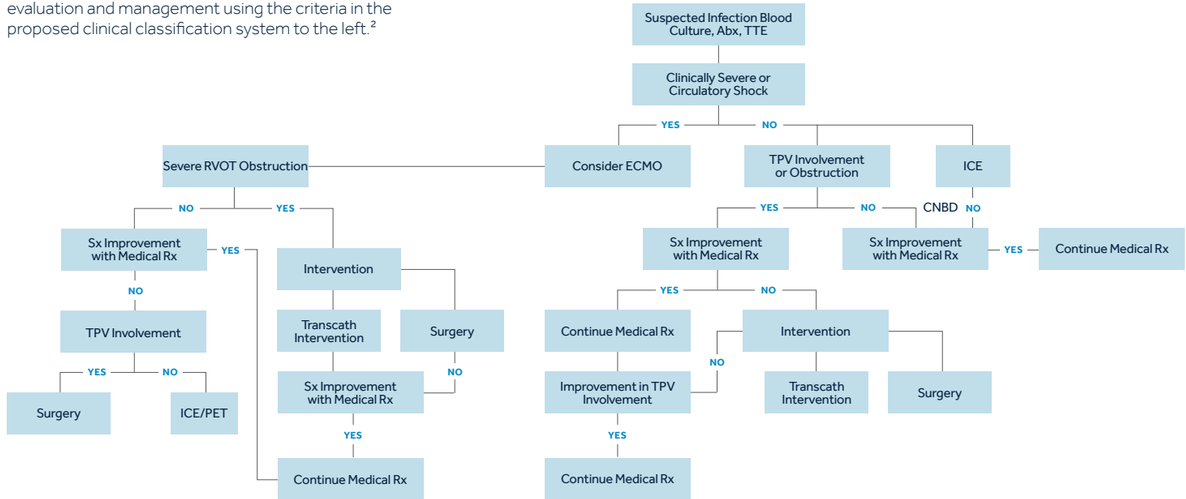
MANAGING ENDOCARDITIS†

The following proposed flow diagram depicts patient evaluation and management using the criteria in the proposed clinical classification system to the left.[2]



Terms:
Abx = Antibiotics
CNBD = Cannot be determined
ECMO = Extracorporeal membrane oxygenation
ICE = Intracardiac echocardiography
PET = Positron emission tomography
RV = Right ventricle
RVOT = Right ventricular outflow tract
Rx = Therapy
Sx = Symptoms
TPV = Transcatheter pulmonary valve
TTE = Transthoracic echocardiography

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References

[1] Medtronic data on file.

[2] McElhinney DB, Sondergaard L, Armstrong AK, et al. Endocarditis After Transcatheter Pulmonary Valve Replacement. *J Am Coll Cardiol.* December 4, 2018;72(22):2717-2728.

[3] Edwards SAPIEN THV IFU. (as of May 2019).

[4] Vezmar M, Chaturvedi R, Lee KJ, et al. Percutaneous pulmonary valve implantation in the young: 2-year follow-up. *JACC Cardiovasc Interv.* April 2010;3(4):439-448.

[5] Lurz P, Coats L, Khambadkone S, et al. Percutaneous pulmonary valve implantation: impact of evolving technology and learning curve on clinical outcome. *Circulation.* April 15, 2008;117(15):1964-1972.

[6] Müller J, Engelhardt A, Fratz S, Eicken A, Ewert P, Hager A. Improved exercise performance and quality of life after percutaneous pulmonary valve implantation. *Int J Cardiol.* May 15, 2014;173(3):388-392.

[7] Kanter KR, Budde JM, Parks WJ, et al. One hundred pulmonary valve replacements in children after relief of right ventricular outflow tract obstruction. *Ann Thorac Surg.* June 2002;73(6):1801-1806; discussion 1806-1807.

[8] Carvalho JS, Shinebourne EA, Busst C, Rigby ML, Redington AN. Exercise capacity after complete repair of tetralogy of Fallot: deleterious effects of residual pulmonary regurgitation. *Br Heart J.* June 1992;67(6):470-473.

[9] Gatzoulis MA, Balaji S, Webber SA, et al. Risk factors for arrhythmia and sudden cardiac death late after repair of tetralogy of Fallot: a multicentre study. *Lancet.* September 16, 2000;356(9234):975-981.

[10] Raikou M, McGuire A, Lurz P, Bonhoeffer P, Wegmueller Y. An assessment of the cost of percutaneous pulmonary valve implantation (PPVI) versus surgical pulmonary valve replacement (PVR) in patients with right ventricular outflow tract dysfunction. *J Med Econ.* 2011;14(1):47-52.

[11] Hayes CJ, Gersony WM, Driscoll DJ, et al. Second natural history study of congenital heart defects. Results of treatment of patients with pulmonary valvar stenosis. *Circulation.* February 1993;87(2 Suppl):I28-37.

[12] Meyer RA, Korfhagen J C, Covitz W, Kaplan S. Long-term follow-up study after closure of secundum atrial septal defect in children: an echocardiographic study. *Am J Cardiol.* July 1982;50(1):143-148.

[13] Kavey RE. Optimal management strategies for patients with complex congenital heart disease. *Circulation.* June 6, 2006;113(22):2569-2571.

[14] Bielefeld MR, Bishop DA, Campbell DN, Mitchell MB, Grover FL, Clarke DR. Reoperative homograft right ventricular outflow tract reconstruction. *Ann Thorac Surg.* February 2001;71(2):482-487; discussion 487-488.

[15] Khanna AD, Hill KD, Pasquali SK, et al. Benchmark Outcomes for Pulmonary Valve Replacement Using the Society of Thoracic Surgeons Databases. *Ann Thorac Surg.* July 2015;100(1):138-145; discussion 145-146.

[16] Baltimore RS, Gewitz M, Baddour LM, et al. Infective Endocarditis in Childhood: 2015 Update: A Scientific Statement From the American Heart Association. *Circulation.* October 13, 2015;132(15):1487-1515.

[17] McElhinney DB. Reflection and Rationalization: Making Sense of the Literature on Endocarditis After Transcatheter Pulmonary Valve Replacement. *Circ Cardiovasc Interv.* February 2017;10(2).e004983.

[18] Lluri G, Levi DS, Miller E, et al. Incidence and outcome of infective endocarditis following percutaneous versus surgical pulmonary valve replacement. *Catheter Cardiovasc Interv.* February 1, 2018;91(2):277-284.

[19] Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. *Circulation.* October 13, 2015;132(15):1435-1486. Erratum in: *Circulation.* October 27, 2015;132(17):e215. *Circulation.* August 23, 2016;134(8):e113. *Circulation.* July 31, 2018;138(5):e78-e79.

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