Transcatheter Pulmonary Valve Implantation

Description

Transcatheter pulmonary valve implantation (TPVI) is an alternative to pulmonary valve replacement by open surgery. It is intended for patients who have previously had a pulmonary valve repair for congenital heart disease, in whom dysfunction of the repaired valve necessitates further intervention.

Background

Description of Disease. Congenital heart disease, including tetrology of Fallot, pulmonary atresia, and transposition of the great arteries, is generally treated by surgical repair at an early age. This involves reconstruction of the right ventricular outflow tract (RVOT) and pulmonary valve by means of a surgical homograft or a bovine-derived valved conduit. These repairs are prone to development of pulmonary stenosis or regurgitation over long periods of follow-up.

As individuals with prior congenital heart disease repair are living longer into adulthood, the problem of RVOT dysfunction following initial repair has become more common. Calcification of the RVOT conduit can lead to pulmonary stenosis, while aneurysmal dilatation can result in pulmonary regurgitation. RVOT dysfunction can lead to decreased exercise tolerance, potentially fatal arrhythmias, and/or irreversible right ventricular dysfunction. (1)

Interventions for RVOT dysfunction often require repeat open heart surgery, resulting in numerous open heart procedures in patients who live into adulthood. Treatment options for pulmonary stenosis, open surgery with valve replacement, balloon dilatation, or percutaneous stenting. (1) Interventions for pulmonary regurgitation are primarily surgical, either reconstruction of the RVOT conduit or replacement of the pulmonary valve through open surgery. The optimal timing of these interventions is not well understood. (2)

Transcatheter pulmonary valve replacement offers a potentially less invasive treatment option for patients with prior surgery for congenital heart disease and RVOT dysfunction. It is possible that the use of less invasive valve replacement techniques can spare patients from multiple repeat open heart procedures over long periods of follow-up.

Description of Technology. The Melody® transcatheter pulmonary valve and the Ensemble® Transcatheter Valve Delivery System are used together for percutaneous replacement of a dysfunctional pulmonary valve. The Melody valve consists of a section of bovine jugular vein with an intact native venous valve. The valve and surrounding tissue is sutured within a platinum-iridium stent
scaffolding. The transcatheter delivery system consists of a balloon-in-balloon catheter with a retractable sheath and distal cup into which the valve is placed. The procedure is performed on the beating heart without use of cardiopulmonary bypass.

The Melody valve is first crimped to fit into the delivery system. It is introduced through the femoral vein and advanced into the right side of the heart and put into place at the site of the pulmonary valve. The inner balloon is inflated to open up the artificial valve, and then the outer balloon is inflated to position the valve into place.

**Regulatory Status**

The Melody® transcatheter pulmonary valve and the Ensemble® Transcatheter Valve Delivery System, manufactured by Medtronic Heart Valves, Inc (Santa Ana, CA), received FDA approval under the Humanitarian Device Exemption (HDE) Program on January 25, 2010. Approval was 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 16mm in diameter when originally implanted; and
- Dysfunctional RVOT conduits with clinical indication for intervention, and either:
  - Regurgitation: ≥ moderate regurgitation; or
  - Stenosis: mean RVOT gradient ≥35mm Hg.

FDA product code: NPV

**Related Policies**

7.01.132 Transcatheter Aortic-Valve Implantation for Aortic Stenosis

**Policy**

*This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.*

Transcatheter pulmonary valve implantation, when performed according to FDA-approved indications, is considered **medically necessary** for patients with prior repair of congenital heart disease and right ventricular outflow tract (RVOT) dysfunction, who are not good candidates for open repair due to one or more of the following conditions:

- High-risk for surgery based due to concomitant medical comorbidities; or
- Poor surgical candidate due to multiple prior thoracotomies for open heart surgery.

Transcatheter pulmonary valve implantation is considered **investigational** for all other non-FDA approved indications.
Rationale

The published literature on TPVI consists of small case series, which generally report on short-term outcomes. Some of the larger, representative publications are discussed in this literature review.

Studies Using FDA-Approved Valves

The only device that currently has U.S. Food and Drug Administration (FDA) approval for transcatheter pulmonary valve implantation is the Melody™ valve (Medtronic Inc., Minneapolis, MN). Approved indications include RVOT dysfunction, defined as pulmonic regurgitation (moderate or greater) or pulmonic stenosis (mean gradient of 35 mm Hg or higher). In addition, a circumferential RVOT conduit should exist that is equal to or greater than 16 mm in diameter when originally implanted.

US Melody TPV Trial. The multicenter US Melody TPV trial is a prospective uncontrolled trial from five clinical sites that was designed to study the safety, procedural success and short-term effectiveness of the Melody transcatheter pulmonary valve. (2, 3) This was the pivotal trial on which FDA approval for the Melody valve was based. This study was designed to follow 150 patients over a five-year period. Eligibility criteria included a dysfunctional right ventricular outflow tract (RVOT) conduit or a dysfunctional bioprosthetic pulmonary valve, plus evidence of heart failure. For patients with New York Heart Association (NYHA) class I heart failure, a Doppler mean gradient of >40mm Hg or severe pulmonary regurgitation was required, and for patients with NYHA class II-IV heart failure, a mean gradient of >35mm Hg or moderate pulmonary regurgitation was required. These inclusion criteria generally were indications for pulmonary valve replacement. The primary outcomes were defined as procedural success, adverse events from the procedure, and effectiveness as measured by the proportion of patients with acceptable valve function at six months.

Interim results from this trial have been published. (2, 3) The most recent publication (2) describing overall outcomes reported on 136 patients who underwent attempted TPVI. A total of 124 of 136 patients (91.2%) had successful implantation. In 12 patients, implantation was not possible due to anatomical or other intra-procedural findings that precluded implantation. One death occurred as a result of the procedure (0.7%), and serious adverse events occurred in 8/136 patients (6%). Adverse events included coronary artery dissection, conduit rupture/tear, wide complex tachycardia, respiratory failure, femoral vein thrombosis, and perforation of the pulmonary artery.

A total of 94 patients had successful implantation and reached the 6-month follow-up time point at the time of publication. Acceptable valve function, defined as mild pulmonary regurgitation or less on echocardiography was present in >90% of patients. Right ventricular pressure and right ventricular outflow tract gradient improved following the procedure, and 71/94 (75.5%) were in NYHA class I heart failure at six months. Over the course of follow-up, stent fractures were diagnosed in 25/124 (20.2%) patients, and 9/124 (7.3%) required implantation of a second valve.

A secondary publication from the US Melody TPV trial focused on the change in exercise function following TPVI. (4) Patients completed a standardized cardiopulmonary regimen 2 months prior to TPVI and 6 months following TPVI. Results of pre- and post- exercise parameters were available for 94-114 patients, depending on the specific outcome. There were numerous physiologic outcome measures
reported, with some of these showing a statistically significant change between the 2 time points, and others not showing a significant change. For example, there was a significant increase in the percent predicted maximal workload from 65.0% at baseline to 68.3% at follow-up (p<0.001) and a significant decrease in the ratio of minute ventilation to CO2 production from 30.8 at baseline to 29.1 at follow-up (p<0.001). In contrast, there were no significant changes in peak oxygen consumption or in spirometric measures of pulmonary function. This study reports modest benefits in exercise parameters for patients treated with TPVI. The results are limited by the lack of a control group and by the large number of patients who did not have completed exercise results available (approximately one-third of total).

Italian Society of Pediatric Cardiology Registry. (5) Butera et al published outcomes of 63 patients who were enrolled in this prospective, multicenter registry. Implantation was successful in 97% (61/63) of patients. There was one early death following TPVI, and peri-procedural complications occurred in 14% (9/63). Two complications were considered major: these were stent migration requiring re-intervention and ventricular fibrillation treated with external cardioversion. The median right ventricular systolic pressure was reduced from 80 at baseline to 20 (p<0.001) following the procedure, and 60% (38/63) of patients had either grade 0 or grade 1 pulmonary regurgitation. At a median follow-up of 30 months, an additional 3 patients died and 6 patients had major complications. These complications included Melody valve endocarditis (n=2), stent fracture requiring re-intervention (n=2), and herpes virus encephalitis (n=2). There were also 8 patients (13%) who had stent fractures that did not require intervention. Freedom from valve failure or re-intervention at last follow-up was estimated to be 81.4%.

Lurz et al. (6) reported on 163 patients who underwent attempted TPVI from 4 clinical centers in Europe. Eligibility for the procedure included elevated RV systolic pressure, increased RVOT dimensions, and either symptoms or evidence of severe RV dysfunction. Procedural success was achieved in 155/163 patients (95.1%). Procedural complications occurred in 12/163 (7.4%), 8 of which were considered serious and 5 of which required open surgery.

The median follow-up was 28.4 months. Over the course of follow-up, 4/155 patients (2.6%) died, and an additional 5/155 patients (3.2%) developed infective endocarditis. At twelve months follow-up, >90% of patients had absent or mild valve dysfunction as measured by echocardiography.

Eicken et al. (7) This study reported on 102 consecutive patients (mean age 21.5 years) undergoing transcatheter pulmonary valve implantation at two centers in Germany. Eligibility for the procedure included RVOT dysfunction with evidence of right ventricular compromise or increased RV pressure. There was one death (1.0%) that occurred as a result of compression of the left coronary artery. Two patients (2.0%) had evidence of stent fracture immediately post-procedure, and one additional patient (1.0%) developed infective endocarditis at 6 months follow-up. At a median follow-up of 357 days, there was a significant decrease in the RVOT gradient from a median of 36mm Hg to 15mm Hg (p<0.0001). However, there was no significant change in exercise capacity as measures by maximal oxygen uptake.

Other case series reported on smaller numbers of patients, with patient populations ranging from 7-59. (8-13) These publications reported generally similar results as the larger series, with high procedural success and relatively low rates of serious complications. One of these trials reports follow-up for up to
2 years; no studies were identified that provide longer follow-up data. One trial reports improvement in quality of life and exercise function following TPV implantation in a series of 59 patients. (13)

Non-FDA Approved Uses of TPVI

There are a variety of potential off-label uses of TPVI that have been reported in the literature. These include use of devices that are not FDA-approved, and use of approved devices for non-FDA-approved indications.

Non-FDA-Approved Indications

A few case series have been reported on use of the Melody valve in patients with clinical characteristics that do not correspond to FDA-approved indications. (14-15) These have included use in valves other than the pulmonic position, patients with conduit sizes that do not correspond to the FDA indications, and patients with prior congenital heart repair surgery that did not involve construction of a right ventricular outflow tract (RVOT) conduit. In general, these case series have reported high rates of procedural success with low rates of peri-procedural complications, but evidence on longer term outcomes is lacking.

Although most studies have evaluated the use of TPV implantation in patients with a constructed RVOT conduit, a few studies have evaluated TPV implantation with either the Melody or Edwards SAPIEN pulmonary valve in a native RVOT or RVOT without a circumferential conduit. Meadows et al reported results from a retrospective, 5-center review of patients who underwent TPV placement in a nonconduit RVOT, with native tissue making up at least part of the circumference. (16) Thirty-one patients were included, with indications for RVOT intervention including primarily valvular insufficiency in 14 (45%), obstruction in 3 (10%), and mixed obstruction and insufficiency in 14 (45%). TPV implantation was successful in all patients, but serious complications occurred in 2 patients (6%). At a median follow up of 15 months (range 1 month-3.8 years), all patients were alive, and no patient had greater than mild pulmonary regurgitation. Among the 19 patients with adequate imaging at follow up, 6 (32%) had evidence of stent fracture. Three patients were treated for endocarditis or bloodstream infection. Malekzadeh-Milani reported outcomes for 34 patients with a native or patched noncircular RVOT who underwent Melody TPV insertion at a single center. (17) The procedure was technically successful in all patients, although early complications occurred in 8.8%. At a mean follow up of 2.6 years, no patients had stent fracture or stent migration, and 32/34 (94.1%) had absent or trivial pulmonary regurgitation.

Several other small case series by Demkow et al (N=10 patients) and Odemis et al (N=7 patients) report on the use of the Edwards SAPIEN pulmonary valve for noncircumferential RVOT patch and large-diameter conduits, respectively. (18,19) The authors report high rates of successful valve implantation, but long term follow up is not reported.

Non-FDA Approved Devices

A small number of retrospective, comparative studies have compared outcomes of the Edwards SAPIEN® pulmonic valve with the Melody® pulmonic valve. Boshoff et al. described the off-label uses in 21 patients treated with the Melody valve and 2 patients treated with the Edwards SAPIEN® pulmonic valve. (15) These included use in native RVOT obstruction, in conduits that were smaller than the FDA-labeled indications, and in large RVOT with a dynamic outflow aneurysm. There were no
deaths or major procedural complications reported for these patients. Clinical outcome data were lacking or very limited in this publication.

Faza et al. reported on 20 patients who underwent successful implantation of the Edwards SAPIEN® pulmonic valve at one clinical center. (20) There were no periprocedural deaths, and all but one patient had no or trivial pulmonic regurgitation on latest follow-up. A comparison of hemodynamic parameters in these 20 patients was made with 13 patients who were treated with the Melody valve. Immediately following the procedure, the transvalvular gradient was similar between groups. At last follow-up, the mean residual transvalvular gradient was higher for patients receiving the SAPIEN® valve (18.4 mm Hg versus 11.2 mm Hg, p=0.016), but this difference was no longer present when patients were matched for length of follow-up.

A few other small case series reporting on the use of the Edwards SAPIEN® Pulmonic Valve for RVOT obstruction have been published. (18, 19, 21, 22)) For example, Kenny et al. reported on a Phase I multicenter study of the Sapien pulmonic valve in 36 patients from 4 clinical centers. (17) Procedural success was reported in 97% of patients. Procedural complications occurred in 19% of patients (7/36), including valve migration (n=3), pulmonary hemorrhage (n=2), ventricular fibrillation (n=1), and stent migration (n=1). At 6-month follow-up there were no deaths and 75% of patients (27/36) were in NYHA class I, compared to 14% at baseline. Freedom from re-intervention at 6 months was 97%.

Adverse Events

In addition to the adverse events reported in the case series, several publications have focused on adverse events following TPVI.

The FDA reviewed results from the US Melody TPV trial as part of the FDA approval process and reported detailed data on complications from the procedure. (23) At that time, data were available for 99 patients enrolled between January 2007 and December 2008. A total of 90 patients were deemed suitable for implantation following catheterization, and 87/90 patients had successful implantation. There was one procedural-related death (1.1%). The following table is adapted from the FDA summary of safety and probable benefit:

### Device-related adverse effects (N=89 subjects)

<table>
<thead>
<tr>
<th>Event</th>
<th>Subjects with Event</th>
<th>Freedom from event at 12mth (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stent fracture (all)</td>
<td>16 (18%)</td>
<td>77.1% (7.5)</td>
</tr>
<tr>
<td>Minor1</td>
<td>11 (12%)</td>
<td>84.1% (6.7)</td>
</tr>
<tr>
<td>Major1</td>
<td>5 (6%)</td>
<td>90.6% (5.2)</td>
</tr>
<tr>
<td>Valve stenosis</td>
<td>6 (7%)</td>
<td>90.5% (4.8)</td>
</tr>
<tr>
<td>Worsening tricuspid regurgitation</td>
<td>1 (1%)</td>
<td>100% (--</td>
</tr>
<tr>
<td>Reintervention2</td>
<td>6 (7%)</td>
<td>93.5% (4.3)</td>
</tr>
<tr>
<td>Reoperation</td>
<td>1 (1%)</td>
<td>98.6% (2.2)</td>
</tr>
</tbody>
</table>

1 Stent fractures that did not require intervention were defined as minor; those that required reintervention were defined as major
2 Reinterventions were balloon angioplasty in one patient; repeat implantation of a second TPV in 5 patients
There were 64 patients in the FDA analysis who reached 6 months of follow-up. Of these, 56/64 (87.5%) had acceptable hemodynamic function of the valve by Doppler echocardiography. At 6 months, approximately 75% of patients were in NYHA class I, and 25% were in NYHA class II. Pulmonary regurgitation that was mild or worse was present in 6.2% of patients.

Another publication focusing on adverse events in the US Melody TPV trial was published in 2011. (20) This publication reported on adverse events at a median follow-up of 30 months in 150 patients. Stent fracture occurred in 26% (39/150) of patients. The estimated freedom from stent fracture was 77% at 14 months and 60% at 39 months. Freedom from re-interventions for all patients was estimated to be 86% at 27 months, and freedom from re-interventions for patients with stent fracture was estimated at 49% at 2 years.

McElhinney reported rates of infective endocarditis from 3 prospective cases series enrolling a total of 311 patients followed for a median of 2.5 years. (25) There were a total of 16 patients (5.1%) diagnosed with endocarditis at any location and 6 patients (1.9%) who had endocarditis at the pulmonic valve location. This corresponded to an annualized rate of pulmonic valve endocarditis of 0.88%/patient-year. Malekzadeh-Milani et al evaluated patients with right-sided infective endocarditis at a single center to evaluate endocarditis rates in patients with TPVs compared with surgically-paced pulmonary valves. (26) Thirty-one patients with right-sided endocarditis and pulmonary valve implantation for congenital heart disease were included. Rates of endocarditis were 1.2 and 3.9 cases/100 person-years in patients with surgically-implanted valves and TPVs, respectively (P=0.03).

Boudjemline et al conducted a prospective observational study to evaluate predictors of conduit rupture during the preparation of the RVOT for TPVI in a cohort of patients over the age of 5 with RVOT obstruction, pulmonary regurgitation, or mixed lesions, who underwent transcatheter therapies, including balloon dilatation, bare metal stent placement, or TPV placement. (27) Ninety-nine patients were included, 56 of whom were adults. Of the total cohort, 83.8% underwent Melody TPV implantation. Conduit rupture occurred in 9 patients (9.09%). In 2 of the 9 patients, conduit rupture was angiographically obvious and severe with extension, causing hemodynamic instability. All conduit ruptures occurred during balloon dilatation, and all occurred in patients with RVOT obstruction. Heavy calcification and the presence of a homograft were associated with conduit rupture risk.

Coronary artery compression during balloon angioplasty or stent placement in the RVOT conduit is considered a relative contraindication to TPV placement. Several studies have evaluated to incidence of coronary artery compression. Morray et al reported the incidence of coronary artery compression in a 4-center series of 404 patients who underwent attempted TPV implantation. (28) Three hundred forty-three patients (85% of total) underwent TPV implantation, and 21 patients (5% of total) had evidence of coronary artery compression. Most patients (N=19) with coronary artery compression did not undergo TPV placement. Using the same cohort reported in the Boudjemline et al study, Fraisse et al reported the incidence, diagnosis, and outcome of coronary compression among patients treated with transcathether RVOT interventions for RVOT obstruction, pulmonary regurgitation, or mixed lesions. (29) All patients underwent balloon dilatation and coronary assessment with angiography, which was followed by TPV placement if there was ongoing RVOT dysfunction. Of 100 patients evaluated, 83% had implantation of a Melody TPV. Coronary artery compression occurred in 6 cases, all of which could
be diagnosed by selective coronary angiogram and/or aortic root angiogram during balloon dilation of the RVOT. No specific risk factors for coronary artery compression were identified.

Ongoing and Unpublished Clinical Trials
A search of the online database ClinicalTrials.gov in September 2014 identified the following interventional trials of TPVI that are currently ongoing:

- Melody® Transcatheter Pulmonary Valve Post-Approval Study (NCT01186692), the Melody Transcatheter Pulmonary Valve (TPV) Post-Market Surveillance Study (NCT00688571), and the Melody Transcatheter Pulmonary Valve Study: Post Approval Study of the Original IDE Cohort (Melody IDE) (NCT00740870) – These are nonrandomized, interventional studies to evaluate the long-term performance of the Melody Transcatheter Valve in patients who underwent transcatheter pulmonary valve implantation for dysfunctional RVOT conduits. For the post-approval study, enrollment is planned for 100 subjects and the estimated study completion date is July 2017. For the post-market surveillance group, enrollment is planned for 63 subjects and the estimated study completion date is December 2014. For the original IDE group, enrollment is planned for 150 subjects and the estimated study completion date is August 2015.
- COMPASSION: COngenital Multicenter Trial of Pulmonic VAValve Regurgitation Studying the SAPIEN Interventional THV (NCT00676689) – COMPASSION is a prospective, nonrandomized, interventional study to evaluate the SAPIEN transcatheter pulmonary valve in patients who previously underwent placement of a conduit between the right ventricle and the pulmonary artery and subsequently developed a dysfunctional RVOT. Enrollment is planned for 70 subjects; the estimated study completion date is March 2018.

Practice Guidelines and Position Statements

In 2014, American Heart Association (AHA) and American College of Cardiology (ACC) issued guidelines for the management of patients with valvular disease. These guidelines do not make specific recommendations regarding the treatment of primary pulmonary valve disease (stenosis or regurgitation), but instead refer to the 2008 guidelines for the management of adults with congenital heart disease. (30)

In 2008, the AHA/ACC issued guidelines for the management of adults with congenital heart disease. For patients with isolated valvular pulmonary stenosis, the guidelines make recommendations regarding balloon valvulotomy or surgical; however, transcatheter pulmonary valve implantation is not addressed. (31)

U.S. Preventive Services Task Force Recommendations

Transcatheter pulmonary valve implantation is not a preventive service.

Summary

There is currently a lack of high-quality evidence evaluating outcomes of this procedure for the indicated population. No randomized controlled trials (RCTs) have been performed, and there are no
controlled trials that compare transcatheter valve implantation to available alternatives. The available evidence consists of case series of patients with RVOT dysfunction who require re-intervention.

The results of the case series indicate that there is a high rate of procedural success and low procedural mortality. The rate of serious procedural adverse events reported in these series ranges from 3.0-7.4%. At 6-12 months of follow-up, there is evidence that the majority of valves demonstrate competent functioning by Doppler echocardiography, with the majority of patients in NYHA functional class I or II. Complications at six months follow-up, such as stent fractures and the need for re-interventions, were reported in an analysis by the FDA to occur at rates of 18% and 7% respectively. Other publications with longer follow-up have reported stent fractures in up to 26% of patients; however the majority of stent fractures have not required re-intervention. There is no direct evidence to demonstrate that TPV implantation leads to a reduction in future open heart procedures.

In patients who are not candidates for open surgery, or who are high-risk for surgery due to other medical co-morbidities, alternative treatment options are limited. Based on the evidence on short-term success, TPVI can be considered medically necessary for patients with prior repair of congenital heart disease and right ventricular outflow tract (RVOT) dysfunction, who are not candidates for open repair, or who are high-risk for open repair.

There is currently limited published evidence on the off-label use of TPVI, including implantation of a non FDA-approved valve, or use of an approved valve for a non FDA-approved indication. The published evidence consists of relatively small case series that are heterogeneous in terms of the device used and the indications for TPVI. For these off-label uses, TPVI is considered investigational.

**Medicare National Coverage**

There is no national coverage decision.

**References**


This policy was approved by the FEP® Pharmacy and Medical Policy Committee on March 20, 2015 and is effective April 15, 2015.

Signature on file

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