



**Australian Government**  
**Department of Health and Ageing**



Australia and New Zealand Horizon Scanning Network

**ANZHSN**

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TERRITORY GOVERNMENTS OF AUSTRALIA  
AND THE GOVERNMENT OF NEW ZEALAND

# **Horizon scanning technology prioritising summary**

## **Percutaneous pulmonary valve implantation**

**November 2009**



**Australian  
Safety  
and Efficacy  
Register  
of New  
Interventional  
Procedures -  
Surgical**



**Royal Australasian  
College of Surgeons**

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ISBN

Publications Approval Number:

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The production of this Horizon scanning prioritising summary was overseen by the Health Policy Advisory Committee on Technology (HealthPACT), a sub-committee of the Medical Services Advisory Committee (MSAC). HealthPACT comprises representatives from departments in all states and territories, the Australia and New Zealand governments; and ASERNIP-S. The Australian Health Ministers' Advisory Council (AHMAC) supports HealthPACT through funding.

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# PRIORITISING SUMMARY

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**REGISTER ID**

**S000102**

**NAME OF TECHNOLOGY**

**PERCUTANEOUS PULMONARY VALVE  
IMPLANTATION**

**PURPOSE AND TARGET GROUP**

**PATIENTS WITH CONGENITAL HEART DEFECTS  
INVOLVING MALFORMATION OF THE RIGHT  
VENTRICULAR OUTFLOW TRACT (RVOT)**

## STAGE OF DEVELOPMENT (IN AUSTRALIA)

- |   |  |
|---|--|
| <input checked="" type="checkbox"/> Yet to emerge | <input type="checkbox"/> Established   |
| <input type="checkbox"/> Experimental             | <input type="checkbox"/> Established <i>but</i> changed indication<br>or modification of technique |
| <input type="checkbox"/> Investigational          | <input type="checkbox"/> Should be taken out of use  |
| <input type="checkbox"/> Nearly established       |  |

## AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

- Yes  
 No  
 Not applicable

## INTERNATIONAL UTILISATION

COUNTRY	LEVEL OF USE		
	Trials Underway or Completed	Limited Use	Widely Diffused
United States	✓		
United Kingdom		✓	

## IMPACT SUMMARY

Percutaneous pulmonary valve implantation (PPVI) is an alternative to stenting for the treatment of a dysfunctional right ventricle to pulmonary artery conduit. The use of PPVI can potentially treat conduit dysfunction without sacrificing valvular competence, and may reduce the need for subsequent surgical repair.

## BACKGROUND

Obstruction of blood flow from the right ventricle to the pulmonary artery, the right ventricular outflow tract (RVOT), is a common feature of a number of congenital heart diseases. In patients with an impaired RVOT, the heart has to work harder than normal to pump blood and is less efficient at returning deoxygenated blood to the lungs. Surgical reconstruction of the RVOT is an integral part of treatment and is one of the most commonly performed operations in patients with congenitally malformed hearts. The repair is usually performed by sewing a cadaveric pulmonary or aortic graft (homograft), a porcine aortic conduit or a bovine jugular vein between the right ventricle and the pulmonary artery to increase the blood flow to the lungs. Dysfunction of the pulmonary valve, which results in pulmonary stenosis and/or backflow of blood (regurgitation), is relatively common post-surgery. Thus, even though surgical placement of conduits is associated a very low mortality rate, the conduits have a relatively short lifespan (less than 10 years) (Lurz and Bonhoeffer 2008). Consequently, patients often require multiple operations during their lifetime to prevent or reverse valvular incompetence or obstruction (Bove et al 1985, Eyskens et al 2000).

In an effort to reduce the need for reoperation, clinicians have utilised percutaneous dilation and stenting (bare-metal stenting [BMS]) to treat degenerated conduits. Although BMS relieves the obstruction to blood flow, it also results in pulmonary valve regurgitation. This was previously thought to be well tolerated in patients, at least in the early stages. However, research has shown that chronic volume overload of the right ventricle as a result of pulmonary valve regurgitation can cause significant right ventricular dysfunction, exercise intolerance and arrhythmia, with the added risk of sudden death (Gatzoulis et al 2000, Frigiola et al 2004).

In 2000, the first pulmonary valve was implanted percutaneously in a 12-year old boy with a dysfunctional RVOT conduit (Bonhoeffer et al 2000). Following this, there has been interest in PPVI as an alternative to BMS. Percutaneous implantation of valves is a rapidly growing field in cardiology; PPVI is similar to percutaneous aortic valve replacement, which was assessed in an earlier prioritising summary written in February 2007. At the time of writing, the only commercially available valve utilised for PPVI is the Melody™ Transcatheter Pulmonary Valve (TPV) (Medtronic Inc., Minneapolis, MN, United States). The Melody valve is a bovine jugular vein valve mounted on a platinum iridium stent that is welded together with gold. The stent is 34 mm long and can be crimped down to a diameter of 6 mm. When expanded, the competence of the tri-leaflet valve is maintained at a large range of diameters, from 12 mm to 22 mm (Lurz et al 2009a). During the implantation procedure, the valve is crimped onto a balloon-in-balloon front-loading delivery system (Ensemble™; Medtronic Inc., Minneapolis, MN, United States), The sheath is constructed from Teflon and the guidewire lumen is braided while a retractable sheath prevents displacement of the valve during delivery. (Lurz and Bonhoeffer 2008).

## **CLINICAL NEED AND BURDEN OF DISEASE**

The Australian Institute of Health and Welfare database indicates that there were a total of 161 pulmonary valve repair or replacement procedures performed from 2006 to 2007. In Australia, the incidence of tetralogy of Fallot is relatively low, with 82 new cases being identified in 2003 (Australian Institute of Health and Welfare 2009).

## **DIFFUSION**

The Melody TPV received the CE mark of approval in October 2006. The United States Food and Drug Administration recommended conditional approval for use of the Melody TPV under a Humanitarian Device Exemption application (H080092) in July 2009 (Medtronic 2009). Devices approved under this exemption are intended for use in fewer than 4000 patients per year in the United States. Currently, the Melody TPV is not approved for use in Australia.

Over 500 PPVIs have been performed worldwide, with over 230 of these being performed in the United Kingdom (Lurz et al 2009a). The Melody TPV post-market surveillance study is currently ongoing and has an enrolment of 63 patients with dysfunctional RVOT conduits. This prospective, multi-centre observational study will assess the long-term clinical performance of the Medtronic Melody TPV over a 5-year period. The expected completion date is August 2014 (ClinicalTrials.gov identifier: NCT00688571). Another study, the Melody TPV feasibility study, was initiated in January 2007 to assess the safety, procedural success, and short-term effectiveness of the TPV in patients with dysfunctional RVOT conduits. The trial is currently recruiting, with a target enrolment of 120 patients. The estimated completion date is January 2014 (ClinicalTrials.gov identifier: NCT00740870) (Clinicaltrials.gov 2009).

## **COMPARATORS**

The comparator to PPVI is percutaneous dilation with BMS. BMS has been shown to decrease right ventricular pressures and potentially prolong the lifespan of conduits, but at the expense of inducing pulmonary regurgitation.

## **SAFETY AND EFFECTIVENESS ISSUES**

### *Study description*

One prospective, non-randomised comparative study on PPVI was identified for inclusion (Lurz et al 2009b), which examined the acute physiological effects of BMS in comparison to PPVI in the perioperative period using an X-ray/magnetic resonance hybrid laboratory. A total of 14 consecutive children (median age 12.9 years, range 9.9 to 17.8) were studied between September 2007 and June 2008. Patients were included if they had a clinical indication for PPVI in the context of significant RVOT obstruction and fulfilled the morphology requirements for PPVI. The majority of patients had tetralogy of Fallot (64%, 9/14) or a similar variant morphology. Patients underwent BMS followed by PPVI, which essentially confounds the results for PPVI due to the presence of BMS. Nevertheless, this study will be discussed due to the paucity of evidence

available on PPVI. Magnetic resonance imaging was utilised before and after both procedures to assess acute physiological changes (Lurz et al 2009b).

Seven prospective case series studies were identified from the literature. All of these publications focused on a group of patients treated with PPVI by a single surgeon at various sites in France and the United Kingdom. The latest and most comprehensive paper on this patient cohort was included (Lurz et al 2008). Between September 2000 and February 2007, a total of 155 patients (median age 21.1 years, range 7 to 71) with RVOT dysfunction underwent PPVI. The majority of these patients had tetralogy of Fallot or one of its variants (61%). Pressure measurements and angiography were performed before and after PPVI. Echocardiographic follow-up was performed at 1, 6, 12, 36 and 70 months post-treatment. The median length of follow up was 28.4 months. The investigators also examined the impact of the learning curve by comparing the results for the first 50 patients with those of the subsequent 105 patients. The rationale for this was that after the 50<sup>th</sup> patient, the device design was finalised and the investigators believed that the learning curve had plateaued in terms of technical experience and patient selection (Lurz et al 2008).

### *Safety*

The comparative study by Lurz et al (2009b) reported no major complications for BMS or PPVI in the perioperative period. In one patient, a guidewire injury resulted in minor lung bleeding. There were no additional details on the incidence of minor complications or the incidence of device related complications during the study.

The case series study by Lurz et al (2008) reported a complication rate of 9% (14/155) over the median 28.4 month follow-up period. Seven of these were considered major complications: device instability in five patients, which included dislodgement of the device (n=2) and homograft rupture (n=3); compression of the left main coronary artery (n=1); and obstruction of the origin of the right pulmonary artery (n=1). Five of the patients with major complications required surgical RVOT revision. During the follow-up period, five patients were diagnosed with endocarditis a median 4.9 months after PPVI, which led to valve removal in three patients. Another patient also required valve removal after developing haemolysis, despite a technically successful valve implantation. The investigators attributed this to a significant residual pressure gradient of 60 mmHg in a small homograft in addition to external compression of the RVOT. A stent fracture led to stent embolisation in the right pulmonary valve in one patient, requiring surgical removal of the Melody valve (Lurz et al 2008).

Four patients died during follow-up, resulting in a survival rate of 96.6% at 83 months post-treatment. PPVI was performed as a palliative procedure in two of these patients who had cardiogenic shock and multiorgan failure at the start of the study. The other two patients died suddenly at 8 and 35 months after the PPVI procedure, presumably due to arrhythmia. Both patients had good valvular competence at their last echocardiographic follow up (Lurz et al 2008).

### *Efficacy*

Lurz et al (2009b) reported that the total procedure, catheterisation and fluoroscopy times were  $209 \pm 14$ ,  $92 \pm 14$  and  $21 \pm 12$  minutes (mean  $\pm$  standard deviation), respectively. The BMS and PPVI procedures were successful in all patients. BMS achieved significant reduction in mean right ventricular systolic pressure (63 vs. 37 mmHg;  $p < 0.001$ ), mean pulmonary artery to right ventricular pullback gradient (43 mmHg vs. 13 mmHg;  $p < 0.001$ ) and the mean ratio of right ventricular to systemic pressure (0.75% vs. 0.41%;  $p < 0.001$ ). However, PPVI did not produce any statistically significant changes in these measurements. In contrast, the mean pulmonary artery diastolic pressure increased significantly after PPVI compared to BMS, indicating that pulmonary valvular competence was restored (9 mmHg before BMS vs. 11 mmHg after PPVI;  $p = 0.048$ ). There were no statistically significant changes in systemic pressures after BMS, although there was a slight but not statistically significant increase after PPVI. Magnetic resonance readings indicated that there was a significant increase in pulmonary regurgitant factor after BMS (21.3% vs. 41.4%;  $p < 0.001$ ) compared to before BMS. In addition, there was a decrease in right ventricular end-systolic volume ( $53.1 \text{ mL/m}^2$  vs.  $41.7 \text{ mL/m}^2$ ;  $p < 0.001$ ) and an increase in total right ventricular stroke volume ( $44.2 \text{ mL/m}^2$  vs.  $56.6 \text{ mL/m}^2$ ;  $p = 0.002$ ) and right ventricular ejection fraction (48.7% vs. 60.7%;  $p < 0.002$ ) as a result of a reduction in ventricular afterload after BMS compared to pre-BMS measurements. Despite these improvements, the lack of overall gain in effective right ventricular stroke volume ( $33.8 \text{ mL/m}^2$  vs.  $32.6 \text{ mL/m}^2$ ) after BMS indicated that these changes did not compensate for the pulmonary regurgitation induced by BMS (Lurz et al 2009b). In contrast, pulmonary regurgitation was virtually eliminated following PPVI as indicated by measurements of pulmonary regurgitation fraction (41.4% after BMS vs. 3.6% after PPVI;  $p < 0.001$ ). Right ventricular end diastolic volume was also significantly lower ( $98.3 \text{ mL/m}^2$  vs.  $85.3 \text{ mL/m}^2$ ,  $p = 0.021$ ) and there was a significant improvement in effective right ventricular stroke volume after PPVI compared with the post-BMS state ( $32.6 \text{ mL/m}^2$  vs.  $41.0 \text{ mL/m}^2$ ;  $p = 0.004$ ). However, there were no significant changes in right ventricular end systolic volume or right ventricular ejection fraction after PPVI, compared with post-BMS measurements (Lurz et al 2009b).

The results of this study indicated that both BMS and PPVI had an effect on left ventricular volumes and function (Lurz et al 2009b). Left ventricular end diastolic volume decreased slightly after BMS but significantly increased after PPVI ( $65.9 \text{ mL/m}^2$  after BMS vs.  $75.4 \text{ mL/m}^2$  after PPVI;  $p < 0.001$ ). Similarly, effective left ventricular stroke volume did not change after BMS, but increased significantly after PPVI ( $33.1 \text{ mL/m}^2$  vs.  $32.5 \text{ mL/m}^2$ ;  $p = 0.013$ ). The significant increase in effective right and left ventricular stroke volume following PPVI was accompanied by a significant reduction in heart rate (75.5 beats per minute vs. 69.0 beats per minute;  $p = 0.006$ ) relative to post-BMS measurements. As a result, there was no significant change in cardiac output after PPVI. During cardiopulmonary exercise testing, the authors noted that peak oxygen uptake increased significantly from 67.6% to 75.7% ( $p = 0.048$ ) (Lurz et al 2009b). However, the relevance of these results is severely limited since PPVI results were confounded by the presence of the BMS.

In the case series study by Lurz et al 2008, the PPVI procedure was successful in 97% (150/155) of patients. The proportion of patients free from surgical revision (reoperation) was  $93 \pm 2\%$ ,  $86 \pm 3\%$ ,  $84 \pm 4\%$  and  $70 \pm 13\%$  at 10, 30, 50 and 70 months, respectively, whereas freedom from transcatheter interventions (balloon dilation or second valve implantation) was  $95 \pm 2\%$ ,  $87 \pm 3\%$ ,  $73 \pm 6\%$  and  $73 \pm 6\%$  at 10, 30, 50 and 70 months, respectively. Re-intervention was required in 7 patients because of conduit obstruction related to the “hammock”<sup>1</sup> effect and in 9 patients owing to stent fractures. The total incidence of stent fractures was 21% in this study. Other reasons for a second valve implantation were restenosis of unknown origin (n=4) and residual RVOT gradient after the first PPVI (n=2). Echocardiography after PPVI showed that there was a significant reduction in mean right ventricular systolic pressure (63 mmHg vs. 45 mmHg;  $p < 0.001$ ) and RVOT gradient (37 mmHg vs. 17 mmHg;  $p < 0.001$ ) compared to baseline values. Post-procedural angiography demonstrated reduced pulmonary regurgitation, which was reflected in an increase in mean diastolic pulmonary artery pressure (10 mmHg vs. 14 mmHg;  $p < 0.001$ ) compared to the baseline measurement. Valvular competence was maintained throughout the follow-up duration and of the 32 patients with data at 36 months after PPVI, 80% had little or no valve regurgitation

The first 50 patients of this cohort required a reoperation earlier than the subsequent 105 patients ( $p < 0.001$ ). Device removal was required in 32% of the first 50 patients, compared with 5% of 105 patients. Similarly, the incidence of a residual RVOT pressure gradient of  $>25$  mmHg was higher in the first 50 patients (32%) compared with the subsequent patients (5%). Residual RVOT pressure gradients of  $>25$  mmHg after PPVI were associated with higher rates of reoperation ( $p = 0.01$ ) and transcatheter reintervention ( $p = 0.008$ ) than gradients of  $<25$  mmHg. The incidence of procedural complications also decreased from 6% (3/50) to 3% (3/105) as the learning curve plateaued. However, freedom from transcatheter reintervention did not decrease with experience as these were predominantly performed to rectify stent fractures, which are not related to the PPVI learning curve.

### **COST IMPACT**

Nordmeyer et al (2006) examined the cost effectiveness of PPVI by comparing models over 25 years for PPVI based on data from 84 patients (with overlaps to Lurz et al 2008) against known costs and outcomes for pulmonary valve replacement in 94 contemporary patients. The model included costs for the initial procedure, complications and reoperations. The investigators noted that earlier studies of PPVI inferred shorter hospital stay, fewer complications and lower mortality. As a result of this, PPVI was more cost effective at all time points relative to surgery despite a higher re-intervention rate. Based on these models, Nordmeyer et al (2006) reported that the PPVI device would have to cost more than US\$33,678 before it becomes more expensive than surgery, while mortality would need to be 25% at 25 years before PPVI lost incremental effectiveness. Assuming all late complications ( $>5$  years) could be treated with a second PPVI, the authors noted that the repeat PPVI rate could reach 17% a year before the procedure

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<sup>1</sup> Refers to incidence where the venous wall of the valve stent hangs into the lumen, causing stenosis. This was observed in the first generation of the Melody TPV, which has been redesigned to address this issue.

became less cost effective relative to surgery. Therefore, the model states that the longevity of the percutaneous valve does not need to match that of surgically implanted valves to retain cost effectiveness (Nordmeyer et al 2006).

However, it is important to note that since the primary data utilised for the assumptions are limited (e.g. overlap with Lurz et al 2008 where results were confounded by presence of BMS), the validity of these cost estimates may be impacted by future, better designed studies on PPVI.

## **ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS**

No issues were identified from the retrieved material.

## **OTHER ISSUES**

Both included studies were performed by the same core researchers. One of the authors is a consultant to Medtronic Inc., the manufacturer of the Melody TPV, and has received honoraria and royalties for this device. In addition to this, two other authors are consultants to and have received honoraria from Medtronic Inc.

## **SUMMARY OF FINDINGS**

Perioperative haemodynamic outcomes from the comparative study (Lurz et al 2009) indicated that PPVI achieves similar improvement to BMS in haemodynamic variables without the problem of pulmonary regurgitation that is associated with BMS. However, the PPVI data was confounded by the presence of a BMS and it is not clear from this study how these improvements affect patient outcomes and reoperation rates.

The case series study (Lurz et al 2008) indicated that PPVI is a feasible procedure (in a select group of patients) and that most patients who underwent PPVI avoided surgical RVOT revision. Nevertheless, the proportion of patients who required re-do procedures (surgical or transcatheter) was quite substantial and increased over time. The results also indicated that patient outcomes improved substantially with operator experience.

## **HEALTHPACT ACTION**

The limited evidence from a single case series study also suggests that PPVI is associated with low mortality rates and is relatively safe with encouraging short term results. There are no data on the longevity of the Melody valve.

The paucity of long-term data is unlikely to be addressed in the near future. However, there is limited evidence that PPVI is feasible despite the high revision rates. It is recommended that PPVI is monitored for 24 months with the view of retrieving some data on the longevity of these valves.

## **NUMBER OF STUDIES INCLUDED**

Total number of studies	2
Level III intervention evidence	1

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**SEARCH CRITERIA TO BE USED**

Pulmonary valve AND ((Percutaneous replacement) OR (Percutaneous implantation))