NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of percutaneous pulmonary valve implantation for right ventricular outflow tract dysfunction

Treating right ventricular outflow tract dysfunction with an artificial valve implanted using a catheter

Right ventricular outflow tract (RVOT) dysfunction is the term given to abnormalities of the pulmonary valve (one of the valves in the heart) and the right ventricular outflow tract. It causes blood to flow abnormally between the heart and the lungs and is often congenital (present from birth). If left untreated RVOT dysfunction can reduce life expectancy. Faulty heart valves are usually replaced during open heart surgery, but with time the replacements can degenerate and fail. Using a catheter to implant an artificial valve is an alternative to further open heart surgery – it is a less invasive procedure because it does not involve opening up the chest. In this procedure, the replacement valve is implanted through a catheter (a narrow tube), which is inserted through the skin and into a large vein in the groin and then into the pulmonary artery. The replacement valve is implanted within a wire mesh tube called a stent.

Introduction

The National Institute for Health and Clinical Excellence (NICE) has prepared this overview to help members of the Interventional Procedures Advisory Committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in May 2012 and updated in September 2012.

Procedure name

- Percutaneous pulmonary valve implantation for right ventricular outflow tract dysfunction

Specialist societies

- British Cardiovascular Intervention Society
- British Cardiovascular Society
- British Paediatric Cardiac Association
- Society of Cardiothoracic Surgeons of Great Britain and Ireland.

Description

Indications and current treatment

RVOT dysfunction often occurs as part of complex congenital heart conditions, such as tetralogy of Fallot. It may take the form of pulmonary valve stenosis, pulmonary valve incompetence (regurgitation) or both. Depending on the severity of the condition and associated structural abnormalities of the heart, RVOT dysfunction causes varying degrees of right ventricular hypertrophy and right heart failure. If left untreated, it can be a life-limiting condition.

Reconstruction of the RVOT, done as part of the surgery for congenital heart disease, is likely to need revision in the long term as a result of growth of the child and/or degeneration of any replacement valve. Normally, revision involves repeat surgery with replacement of the RVOT and/or any previously placed conduit.

Percutaneous pulmonary valve implantation (PPVI) is an interim alternative to surgery for some patients. This approach is usually used for patients who have had a previous RVOT conduit or valve replacement. Many of the patients with this condition are adolescents or young adults, who may need multiple valve replacement procedures during their lifetime.

What the procedure involves

The aim of PPVI is to provide a less invasive intervention than open heart surgery to improve pulmonary valve function and circulation to the lungs while reducing the pressure in the right ventricle. The treatment strategy may be to delay the need for further surgical revision.

The procedure is done with the patient under general anaesthesia. PPVI is done by inserting a catheter system through a large vein (typically the femoral vein). Angiography is used to identify the anatomy of the RVOT and its relation to coronary arteries. A stent-mounted valve is introduced over a guidewire and is positioned in the RVOT, under fluoroscopic guidance. A balloon is then inflated to deploy the valve. Sometimes a plain stent is inserted first to dilate the RVOT and provide a regular surface onto which the stent-mounted valve can be fixed. This may decrease the risk of

stent fracture, and thereby increase the longevity of the valve. The procedure can be repeated if necessary.

Most valves used in this procedure are derived from animal sources.

Clinical assessment

Commonly used measures to characterise the severity of the condition include:

- New York Heart Association (NYHA) heart failure classification:

  I− no limitation of physical activity

  II – mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity

  III – marked limitation in activity due to symptoms, even during less-than-ordinary activity, for example walking short distances (20–100 m). Comfortable only at rest.

  IV − inability to carry out any physical activity without physical discomfort.
- right ventricular diameter (on echocardiography)
- right ventricle to pulmonary artery pressure gradients
- regurgitation severity (based on echocardiographic criteria)

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to Percutaneous pulmonary valve implantation for right ventricular outflow tract dysfunction. Searches were conducted of the following databases, covering the period from their commencement to 25 September 2012: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with right ventricular outflow dysfunction
Intervention/test	Percutaneous pulmonary valve implantation
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the overview

This overview is based on 599 patients from 1 non-randomised comparative study[1] and 7 case series[2-8] (this is likely to be an overestimate as there appears to be some patient overlap in the included studies). Safety data from the UK Cardiac Central Cardiac Audit Database have also been included[9].

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A.

Table 2 Summary of key efficacy and safety findings on percutaneous pulmonary valve implantation for right ventricular outflow dysfunction

Abbreviations used: APV, absent pulmonary valve syndrome; BMS, bare metal stent; CT, computed tomography; IQR, interquartile range; MRI, magnetic resonance imaging; NR, not reported; PA, pulmonary artery; PI, pulmonary insufficiency; PPVI, percutaneous pulmonary valve implantation; PVR, pulmonary valve replacement; RV, right ventricle; RVOT right ventricular outflow tract; SD, standard error; SEM, standard error of the mean; TGA, transposition of the great arteries; ToF, Tetralogy of Fallot; TTE, transthoracic echocardiography; VSD, ventricular septal defect; VT, ventricular tachycardia

Study details

Nordmeyer J (2011)[1]

Non-randomised comparative study

UK

Recruitment period: 2005-08

Study population: Patients with congenital heart disease. Aetiology: Majority of the patients had primary diagnosis pulmonary atresia with VSD (33%) and ToF (31%)

Number of previous interventions : median 2 (range 1 to 6) in the PPVI only group and median 2.5 (range 1 to 5) in the presenting group. Timing from last intervention to PPVI not reported.

n=**108 (54 PPVI only vs 54 with pre-**

Key efficacy findings

Number of patients analysed: **106 (52 vs 54)**

Cardiac function

Change between pre and post procedure.

Parameter		PPVI n=52	Pre-stenting with BMS+PPVI N=54	p-value between groups
RV systolic pressure	Baseline	57 ± 16	65 ±23	NR
	Change	-16± 15	-24±22	0.02
	Post procedure	42 ±11[a]	41 ± 13[a]	NR
RV end diastolic pressure	Baseline	11±4	12±5[b]	NR
	Change	-3 ±4	-2 ±3[b]	0.29
RV-to-systemic pressure ratio (%)	Baseline	63 ±18	72± 25	NR
	Change	-21 ±16	-33 ±23	0.004
PA systolic pressure	Baseline	28± 9[c]	25±8	NR
	Change	2 ± 8[c]	3±10	0.85

Key safety findings

Procedural complications

Complication	PPVI	BMS + PPVI
RVOT conduit rupture (no further details)	2 (1 patient with significant bleeding after conduit rupture requiring emergency surgery)	1 (no further details)
Complete obstruction of the right PA	1 (requiring emergency surgery)	0
Significant bleeding after guidewire injury	0	1 (treated by emergency placement of a covered stent to the left PA)
Damage of tricuspid valve chordae	0	3
Arrhythmia	3 (non-sustained VT)	2 *(sustained VT requiring defibrillation)
Rupture of high pressure balloon at post dilation	0	3

Comments

Follow-up issues:

- 13% (14/108) loss to follow-up. Reasons: deaths (n=3), device explantations (n=4), repeat PPVI (n=2) and 'lost to follow-up' (n=5). It is unclear how many of the patients lost to follow up were in the 'PPVI only' or in the 'presenting with BMS' group.
- Results for cardiopulmonary exercise testing and pulmonary regurgitation factor available for only a subset of patients.

Study design issues:

- Patients assigned to treatment groups in a non-randomised fashion, taking into account that pre-stenting was

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<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>stenting with BMS before PPVI)
Age: mean 22 years
Sex: 61% male

Patient selection criteria: Study reported ‘no uniform inclusion criteria’ was applied.

Technique: Under general anaesthesia, access was obtained through the femoral vein in most patients. A stent mounted bovine valve (Melody®, Medtronic) was deployed and the position confirmed by angiography.
Pre-stenting with BMS was performed using balloon-expandable stents in majority (96%) of patients.
Follow-up: 1 year
Conflict of interest/source of funding: Three</td>
<td>Data reported as mean ±SD and units in mmHg unless otherwise noted; [a] p<0.0001between baseline and post-procedure [b]data reported for n=52; [c]data reported for n=51
RV-to-PA pressure gradients (patients stratified into 3 subgroups defined by pre-procedural RV-to-PA gradients):
Subgroup: ‘mild’ RV-to-PA gradient (0-25 mmHg)
<table>
<tr><th></th><th>PPVI
n=23</th><th>Pre-stenting with BMS+PPVI
n=12</th><th>p-value</th></tr>
<tr><td>Pre-procedure RV-to-PA gradient (mmHg)</td><td>15± 7</td><td>15 ±7± 1.6
(as reported)</td><td>0.84</td></tr>
<tr><td>Change in RV-to-PA gradient
(mmHg)</td><td>-5 ±6</td><td>-5 ±8</td><td>0.81</td></tr>
</table>
Subgroup: ‘moderate’ RV-to PA gradient (26-40 mmHg)
<table>
<tr><th></th><th>PPVI
N=16</th><th>Pre-stenting with BMS+PPVI
N=17</th><th>p-value</th></tr>
<tr><td>Pre-procedure RV-to-PA gradient (mmHg)</td><td>34± 5</td><td>33± 4</td><td>0.37</td></tr>
</table>
Subgroup: ‘high’ RV-to PA gradient (>40 mmHg)</td>
<td>Study reported no significant difference in procedural complications (not requiring emergency surgery or catheter intervention) between the two groups. (p=1.00)
Serious adverse events:
<table>
<tr><th>Complication</th><th>PPVI</th><th>BMS + PPVI</th></tr>
<tr><td>Death</td><td>2 (1 patient died after a chest infection at 2 months; ‘presumed arrhythmia’ at 24 months in 1 patient with pulmonary hypertension)</td><td>2 (pulmonary oedema at 1 day after the procedure in 1 patient ‘presumed‘ arrhythmia at 8 months in 1 patient after Rastelli repair;)</td></tr>
<tr><td>Endocarditis</td><td>1 (treated by device explantation and surgical RVOT revision at 19 months)</td><td>2 (treated by device explantation and surgical RVOT revision at 5 months in 1 patient because of RVOT severely fractured BMS proximal to the PPVI and subsequent</td></tr>
</table></td>
<td>intended to provide anchoring support for subsequent PPVI in some patients (for example, for those with native or patch-extended RVOT).
• Follow-up outcome assessment not blinded.
• Multivariate analysis for risk of developing stent fractures was adjusted for the following factors: native or patch-extended RVOT, fluoroscopically visible RVOT calcifications, post-dilation of PPVI with high pressure balloon, pre-stenting with BMS, ‘important’ acute PPVI recoil, direct apposition of PPVI and the anterior chest wall.
• Type of stent fracture classified as type I (no loss of</td>
</tr>
</table>

Abbreviations used: APV, absent pulmonary valve syndrome; BMS, bare metal stent; CT, computed tomography; IQR, interquartile range; MRI, magnetic resonance imaging; NR, not reported; PA, pulmonary artery; PI, pulmonary insufficiency; PPVI, percutaneous pulmonary valve implantation; PVR, pulmonary valve replacement; RV, right ventricle; RVOT right ventricular outflow tract; SD, standard error; SEM, standard error of the mean; TGA, transposition of the great arteries; ToF, Tetralogy of Fallot; TTE, transthoracic echocardiography; VSD, ventricular septal defect; VT, ventricular tachycardia

Study details

authors are consultants to manufacturer and one has ownership interest with Melody valve. Three authors have received honoraria from the manufacturers. Authors supported by government and charitable funding

Key efficacy findings

	PPVI N=12	Pre-stenting with BMS+PPVI N=20	p-value
Pre-procedure RV-to-PA gradient (mmHg)	52± 9	53± 10	0.86
Change in RV-to-PA gradient (mmHg)	-36 ±15	-39 ±8	0.56

Pulmonary regurgitation fraction

In a subset of patients 64% (69/108) who underwent paired cardiac MRI the pulmonary regurgitation fraction decreased in both groups

	Pre procedure (%)	After PPVI (%)	p-value
PPVI	25	2	<0.001
Pre-stenting with BMS+PPVI	20	3	<0.001

Study reported that the change in pulmonary regurgitation fraction was not significantly different between the two treatment groups (p=0.15).

Key safety findings

		endocarditis] and 15 months in another patient)
RVOT Pseudo aneurysm	1 (treated by device explantation at 16 months)	0
Recurrent RVOT obstruction	4 (treated by repeat PPVI because of stent fractures at 6,16 and 24 months in 3 patients; in-stent stenosis of unknown origin at 2 months in 1 patient)	1(treated by repeat PPVI at 18 months)

Freedom from serious adverse events (death, device explantation, repeat PPVI) was not significantly different at 1 year: 92% 'PPVI only' group vs 94% 'pre-stenting and PPVI' group (p=0.44).

Stent fractures

Type I stent fractures: 23.1% (12/52) in the PPVI only group and 17.3% (9/52) of patients in the pre-stenting group.

Type II stent fractures: 5.8% (3/52) in the PPVI only group.

Comments

stent integrity), type II (loss of restenosis on echocardiography) and type III (separation of fragments or embolization)

- P-values reported for peak RVOT velocities are based on two-way analysis of variance analysis.
- Only a subset of patients analysed for cardiopulmonary exercise testing and cardiac MRI assessments (reasons not reported)

Study population issues:

- Significant RVOT obstruction (n=60) and significant pulmonary regurgitation (n=60) was reported (suspect there is an error in numbers reported)
- No significant

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Study details	Key efficacy findings	Key safety findings	Comments
	Exercise testing In a subset of patients 64% (69/108) underwent paired cardiopulmonary exercise testing (peak VO_2). In patients with 'mild' (0-25 mmHg) and 'severe' (>40 mmHg) RVOT obstruction, the change in peak VO_2 was not significantly different between the treatment groups (absolute figures not reported; mild: p=0.35; severe: p=0.59) In patients with 'moderate' (26-40 mmHg) RVOT obstruction, patients who had pre-stenting had a significantly greater acute change in peak VO_2 *(3.5 ±3.9 ml/kg/min) compared with 'PPVI only' group (-0.2 ±3.8 ml/kg/min) (p=0.03) **Peak RVOT velocities** Of 91% (86/94) who underwent echocardiographic follow-up at 1 year: ● patients in the 'mild' RVOT obstruction subgroup (0-25 mmHg), there was no significant difference in peak RVOT velocities between the two treatment groups. ● patients with 'moderate' (26-40 mmHg) or 'severe' (>40 mmHg) RVOT obstruction subgroups showed a lower peak RVOT velocities compared with patients in PPVI 'only' group ('moderate': p=0.01;'severe': p=0.045).	Prestenting with BMS was associated with a reduced risk of developing PPVI stent fracture (HR 0.35, 95% CI 0.14 to 0.87, p=0.024). Factors significantly associated with an increased risk of developing PPVI stent fractures were : significant PPVI recoil (HR 4.4, 95% CI 1.9 to 10.3, p=0.001) and direct apposition of the valve and the anterior chest wall (HR 4.0, 95% CI 1.7 to 9.6, p=0.002).	difference in age, sex, principal diagnosis. • The pre-procedural RV-to-PA pressure gradient was significantly different (p=0.02) at baseline with a higher RV-to-PA pressure gradient in the pre-stenting group. For analysis, patients were stratified into three subgroups (mild, moderate, severe). • Number of patients with native or patch-extended compared with the PPVI only group(13% vs 0%; p=0.01). **Other issues**: • Associated procedures (for example, coarctation stenting) was undertaken in 17% of the patients.

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Study details

Lurz P (2008) [2]

Case series

Multicentre study

UK and France

Recruitment period: 2000-07

Study population: Patients with stenosis (41%), regurgitation (31%) or both. Most patients had ToF (61%) or a variant morphology; 92% had an RV-to-PA conduit placed at previous surgery, 81% of which were homografts.

n=**155**

Age: median 21 years

Sex: 58% males

Patient selection criteria: RV systolic pressures >2/3 of systemic plus symptoms or RV systolic pressures>3/4 of systemic in absence of symptoms and/or moderate or severe PR and 1 of the

Key efficacy findings

Number of patients analysed: **155**

Survival rate

96.6% survival rate was reported at 83 months after the procedure.

Cardiac function

	Preoperative (n=155)	Postoperative (n=155)
RV systolic pressure	63 ±18	45± 13
RV end diastolic pressure	12 ±4	10 ±5
RV-to-PA gradient	37± 20	17 ±10
PA diastolic pressure	10± 4	14± 9
RV-to-systemic pressure (%)	69 ±19	45± 14

Unless noted otherwise, all values are reported as mean ±SD (units: mmHg). The difference was statistically significant between the two time points at p<0.001. Study also reported data separately for patients who were 'predominantly stenosis', 'predominantly regurgitant' or 'combined lesions'.

Freedom from transcatheter reinterventions (n=155)

Timing (months)	% ±SEM
10	95± 2
30	87± 3
50	73± 6
70	73 ±6

Key safety findings

Major procedural complications	**n**
Device instability, including dislodgment of the device (no further details)	2
Homograft rupture (led to neurological sequelae because of prolonged resuscitation in 1 patient; 1 patient required surgery for haemostasis but valved stent conserved)	3
Compression of the left main coronary artery after device deployment (no further details)	1
Obstruction of the origin of the right PA (no further details)	1
Guidewire injury of the distal PA with minor bronchial bleeding (no further details)	2
Partial homograft rupture (led to confined extravasation of contrast medium)	1
Moderate tricuspid regurgitation (caused by damage to tricuspid valve by the balloon of delivery system)	2

Of the 12 patients, 5 patients who had major complications needed surgical RVOT revision; details on how the remaining patients were treated was not reported. None led to death.

Complications during follow-up

1 patient developed haemolysis 'within hours' after the procedure requiring device explantation.

2.6% (4/155) died. 2 were presumed to be related

Comments

There may be some duplication of data presentation with Nordmeyer 2011

Follow-up issues:

- Follow-up was 100% complete for the outcomes death, reoperation and transcatheter interventions. Reasons for loss to follow-up was not reported for the remaining outcomes

Study design issues:

- Methods used to recruit patients not described
- Reoperation and transcatheter reintervention-free survival calculated from date of valve implantation to latest follow-up or date of surgery/ catheterisation (expressed as percentage ±SEM).

Abbreviations used: APV, absent pulmonary valve syndrome; BMS, bare metal stent; CT, computed tomography; IQR, interquartile range; MRI, magnetic resonance imaging; NR, not reported; PA, pulmonary artery; PI, pulmonary insufficiency; PPVI, percutaneous pulmonary valve implantation; PVR, pulmonary valve replacement; RV, right ventricle; RVOT right ventricular outflow tract; SD, standard error; SEM, standard error of the mean; TGA, transposition of the great arteries; ToF, Tetralogy of Fallot; TTE, transthoracic echocardiography; VSD, ventricular septal defect; VT, ventricular tachycardia

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>following: symptoms, severe RV dysfunction, severe RV dilatation, impaired exercise capacity. Morphological criteria
RVOT dimensions < 22x22mm or >14x14mm. Exclusion criteria; pregnancy, occluded central veins, active infection and weight <20kg.
Technique: Under general anaesthesia, using a femoral venous approach in majority of the cases (transjugular access in 7 patients) valve (Melody®, Medtronic) implantation was performed. All PPVI performed by a single operator.
Follow-up: median 28 months (range 0 to 83 months)
Conflict of interest/source of funding: Three authors are</td>
<td>Freedom from reoperation (n=155)
<table><tr><td>Timing (months)</td><td>% ±SEM</td></tr><tr><td>10</td><td>93± 2</td></tr><tr><td>30</td><td>86± 3</td></tr><tr><td>50</td><td>84± 4</td></tr><tr><td>70</td><td>70 ±13</td></tr></table>RVOT gradient (after second PPVI)
Second PPVI led to significant decrease in RVOT gradient (from 47.6± 18.2 to 19.5± 10.0 mmHg, p<0.001).
Pulmonary regurgitation
‘Moderate’ pulmonary regurgitation was observed in 2 patients (with endocarditis) All patients had ‘mild’ or less pulmonary regurgitation at a median follow-up of 18.5 months.
Peak RVOT velocity
<table><tr><th>Timing</th><th>Peak RVOT velocity (m/s); n</th></tr><tr><td>Before PPVI</td><td>3.67± 0.85 (n=151)</td></tr><tr><td>1 month after PPVI</td><td>2.84 ±0.7 (n=143)</td></tr><tr><td>6 months after PPVI</td><td>2.93± 0.74 (n=109)</td></tr><tr><td>12 months after PPVI</td><td>2.91 ±0.74 (n=104)</td></tr><tr><td>36 months after PPVI</td><td>3.17 ±0.86 (n=32)</td></tr><tr><td>70 months after PPVI</td><td>3.70± 1.31 (n=3)</td></tr></table>Data reported as mean± SD. Study also reported results separately for peak RVOT velocity in ‘patients without any intervention after PPVI’ and in ‘reoperated/recatheterised</td>
<td>to arrhythmia (at 8 and 35 months after PPVI), 1 patient died of pulmonary oedema 24 hours after the procedure and 1 patient died of chest infection (approximately 6 weeks after PPVI).
Incidence of stent fractures was 21% (absolute figures not reported) requiring reintervention in 9 patients, Stent embolisation into the right PA (because of stent fractures) was reported in 1 patient. Patient needed surgical explantation of the percutaneous pulmonary valve.
Endocarditis (diagnosed median 4.9 months after PPVI) occurred in 5 patients; led to valve explantation in 3 patients, successfully treated medically in 2 patients.
Ventricular tachycardia was reported in 1 patient (3.5 years after the procedure; resuscitated successfully without neurological sequelae).
Reinterventions were performed in 22 patients: second valve implantation with a stent-in-stent technique (n=19) and balloon dilatation of the device (n=3). Reasons for second PPVI were ‘hammock’ effect (n=7), stent fractures (n=9), unknown origin (n=4) and residual RVOT gradient after the first procedure (n=2).
Explantation of device
Explantation of the device was performed in 23 patients (5 patients underwent re-implantation in the same cohort).</td>
<td>• To determine learning curve, 2 cohorts were defined: cohort consisted of the first 50 patients and a second cohort representing the next 150 patients
Study population issues:
• Patients with RVOT gradient >50 mmHg and less than moderate pulmonary regurgitation on echocardiography were classified as ‘predominantly stenosis’. Patient with RVOT gradient <50mmHg and at least ‘moderate’ pulmonary regurgitation on echocardiography were categorised as ‘predominantly regurgitant’. Patients who did not fit either category were categorised ‘combined lesions’</td>
</tr>
</table>

Abbreviations used: APV, absent pulmonary valve syndrome; BMS, bare metal stent; CT, computed tomography; IQR, interquartile range; MRI, magnetic resonance imaging; NR, not reported; PA, pulmonary artery; PI, pulmonary insufficiency; PPVI, percutaneous pulmonary valve implantation; PVR, pulmonary valve replacement; RV, right ventricle; RVOT right ventricular outflow tract; SD, standard error; SEM, standard error of the mean; TGA, transposition of the great arteries; ToF, Tetralogy of Fallot; TTE, transthoracic echocardiography; VSD, ventricular septal defect; VT, ventricular tachycardia

Study details	Key efficacy findings	Key safety findings	Comments
consultants to manufacturers and have received honoraria	patient'.	**Reason for explantation** / **n** Residual stenosis: 6 Endocarditis: 3 Outgrown conduit: 3 Venous wall hanging in the stent ('hammock' effect) causing stenosis (combined with stent fracture or external compression): 4 Valve dislodgement: 2 Left coronary artery compression: 1 Obstruction of right pulmonary artery: 1 Homograft rupture: 1 Stent fractures (late embolisation): 1 Increasing gradient across mechanical aortic valve: 1 Of the patients who underwent device explantation, 16 patients were in the first series of 50 patients. 34.7% (8/23) of patients with explanted device had the first generation of the device.	• Patients were classified as NYHA functional class 1(11%), II (52.9%), III (29.0%) and IV (7.1%). **Other issues**: • Procedures were performed over a time frame greater than 6 years. During this period, different generations of Melody valve were developed. It is unclear how many patients received a1st generation or 2nd generation valve • Authors noted an impact of learning curve on outcomes.

Abbreviations used: APV, absent pulmonary valve syndrome; BMS, bare metal stent; CT, computed tomography; IQR, interquartile range; MRI, magnetic resonance imaging; NR, not reported; PA, pulmonary artery; PI, pulmonary insufficiency; PPVI, percutaneous pulmonary valve implantation; PVR, pulmonary valve replacement; RV, right ventricle; RVOT right ventricular outflow tract; SD, standard error; SEM, standard error of the mean; TGA, transposition of the great arteries; ToF, Tetralogy of Fallot; TTE, transthoracic echocardiography; VSD, ventricular septal defect; VT, ventricular tachycardia

Study details

McElhinney DB (2010) [3]

Case series

USA

Multi-centre study (Melody ® valve IDE trial)

Recruitment period: 2007-09

Study population: Patients with dysfunctional RVOT conduits or bioprosthetic pulmonary valves.

n=**136**

Age: median 19 years

Sex: 64% males

Patient Inclusion criteria; aged 5 years or above, weight more than 30 kg, echocardiographic evidence

of RVOT conduit dysfunction. Exclusion criteria:

acute endocarditis, major progressive

Key efficacy findings

Number of patients analysed: 124

Cardiac function (during catheterisation)

In patients with primary indication pulmonary regurgitation (n=65):

	Pre-implant	Post-implant	p-value
RV systolic pressure	61.6± 20.6	47.2 ±15.0	0.001
Peak RV – to-PA gradient	28.1± 15.7	12.7± 7.4	0.001
PA systolic pressure	34.8 ±14.6	34.9± 13.1	0.94

Data reported as mean ± SD (units mmHg)

In patients with primary indication obstruction or mixed (n=59):

	Pre-implant	Post-implant	p-value
RV systolic pressure	69.4 ± 12.9	44.7 ±10.9	0.001
Peak RV – to-PA gradient	43.7± 11.4	14.4± 5.7	0.001
PA systolic pressure	30.1 ±16.8	31.5± 11.1	0.9

Key safety findings

Serious procedural adverse events : 6% (8/136)

Complication	n
Death (within 30 days)	1 (in patient with coronary artery dissection and subsequent intracranial haemorrhage)
Conduit rupture	1 (treated by replacement conduit)
Conduit rupture/tear	1 (treated by covered stent placement)
Tachycardia	1 (treated by cardioversion)
Hypercarbia and elevation of LV filling pressure	1 (treated by milrinone and mechanical ventilation)
Femoral vein thrombosis	1 (treated by anticoagulation, thrombolysis and balloon angioplasty)
Perforations of a distal pulmonary artery branch (caused by guidewire)	2 (1 patient treated by coil occlusion of the injured vessel; 1 'self-limited').

7 patients were discharged within 1 week of implantation

Stent fractures

Stent fractures were reported in 18% (25/136) patients (timing between 2 months to 2 years). All but 1 fracture was defined as minor (≥1 individual

Comments

Follow up issues:

- 8.8% loss to follow-up. In 12 patients implantation was not attempted because of risk of coronary compression (n=6), insufficient RVOT obstruction (n= 3 patients with stenosis), anatomically unsuitable conduit (n=2) and indication for concomitant pulmonary artery stenting (n=1; disallowed in the initial version of the protocol).

Study design issues:

- Number of patients included in analysis varied depending on the outcome or time of follow-up.

Study population issues:

- 48% of patients had ToF as the primary cardiac diagnosis.

Abbreviations used: APV, absent pulmonary valve syndrome; BMS, bare metal stent; CT, computed tomography; IQR, interquartile range; MRI, magnetic resonance imaging; NR, not reported; PA, pulmonary artery; PI, pulmonary insufficiency; PPVI, percutaneous pulmonary valve implantation; PVR, pulmonary valve replacement; RV, right ventricle; RVOT right ventricular outflow tract; SD, standard error; SEM, standard error of the mean; TGA, transposition of the great arteries; ToF, Tetralogy of Fallot; TTE, transthoracic echocardiography; VSD, ventricular septal defect; VT, ventricular tachycardia

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>non-cardiac disease

Technique: Under general endotracheal anaesthesia, patients underwent cardiac catheterisation. Conduit pre-dilation was performed in all patients. Following valve implantation post-dilations of the valve was done at the discretion of the operator. All patients received heparin and antibiotic prophylaxis during and after the procedure.

Follow-up: 2 years
Conflict of interest/source of funding: Trial sponsored and funded by Medtronic. Authors acted as consultants investigators and/or proctors.</td>
<td>Exercise testing
<table>
<tr><th></th><th>Pre-implant (n=113)</th><th>6 months (n=93)</th><th>p-value</th></tr>
<tr><td>Oxygen uptake (peak relative VO_2)(ml/kg/min)</td><td>23.9± 8.6</td><td>24.5 ±7.8</td><td>0.44</td></tr>
<tr><td>Respiratory exchange ratio</td><td>1.11± 0.12</td><td>1.13± 0.12</td><td>0.01</td></tr>
</table>
Data reported as mean ± SD. There may be an error in the reported p- value for the outcome respiratory exchange.
NYHA functional class
<table>
<tr><th></th><th>Pre-implant (n=124)</th><th>6 months (n=94)</th><th>1 year (n=62)</th><th>2 years (n=24)</th></tr>
<tr><td>I</td><td>19</td><td>71</td><td>47</td><td>18</td></tr>
<tr><td>II</td><td>86</td><td>23</td><td>15</td><td>6</td></tr>
<tr><td>III</td><td>18</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>IV</td><td>1</td><td>0</td><td>0</td><td>0</td></tr>
</table>
Pulmonary regurgitation
Pulmonary regurgitation (assessed on echocardiograph) was ‘moderate’ or ‘severe’ before implantation in 81% of patients (absolute figures not reported) and was graded as ‘none’ or ‘trivial’ in more than 90% (absolute figures not reported) of patients at follow-up.</td>
<td>struts fractured but no loss of stent integrity) initially. 6 patients progressed from minor to major (defined as multiple strut fractures with a loss of stent integrity). 8 patients were treated by reintervention.

Reinterventions
10 patients underwent reinterventions involving the valve (9 valve-in-valve because of stent fracture and recurrent RVOT obstruction; 1 balloon dilatation because of recurrent RVOT obstruction).

NYHA functional class
Functional status declined in 5 patients from NYHA Class I to II (3 associated with stent fracture and recurrent RVOT obstruction) from pre-implantation to 2 years follow-up.</td>
<td>48% had more than 1 prior surgical conduits.
• 76% of patients had homografts, 19% had bioprosthetic valve or valved conduit, and 5% synthetic conduit.

Other issues:
• This study is an interim report of McElhinney (2011)[4] included in table 2 and a follow-up of one study (Zahn 2009) included in Appendix A.
• There were successive recruitment phases for this study, with different eligibility criteria.
• Concomitant procedures which were not permitted in the first 35 implanted patients were subsequently allowed in 89 patients. Follow-up protocol has been</td>
</tr>
</table>

Abbreviations used: APV, absent pulmonary valve syndrome; BMS, bare metal stent; CT, computed tomography; IQR, interquartile range; MRI, magnetic resonance imaging; NR, not reported; PA, pulmonary artery; PI, pulmonary insufficiency; PPVI, percutaneous pulmonary valve implantation; PVR, pulmonary valve replacement; RV, right ventricle; RVOT right ventricular outflow tract; SD, standard error; SEM, standard error of the mean; TGA, transposition of the great arteries; ToF, Tetralogy of Fallot; TTE, transthoracic echocardiography; VSD, ventricular septal defect; VT, ventricular tachycardia

Study details	Key efficacy findings	Key safety findings	Comments
			amended to eliminate monthly visits and computed tomography pulmonary angiography evaluation. • Concomitant interventions included bare metal stenting of RVOT (n=43), branch pulmonary artery stenting or angioplasty (n=8) coronary artery stenting (n=1) inferior vena cava stenting (n=1) and atrial septal defect closure (n=1). • Information on anticoagulant treatment reported in the interim report (Zahn 2009) included in appendix A.

Abbreviations used: APV, absent pulmonary valve syndrome; BMS, bare metal stent; CT, computed tomography; IQR, interquartile range; MRI, magnetic resonance imaging; NR, not reported; PA, pulmonary artery; PI, pulmonary insufficiency; PPVI, percutaneous pulmonary valve implantation; PVR, pulmonary valve replacement; RV, right ventricle; RVOT right ventricular outflow tract; SD, standard error; SEM, standard error of the mean; TGA, transposition of the great arteries; ToF, Tetralogy of Fallot; TTE, transthoracic echocardiography; VSD, ventricular septal defect; VT, ventricular tachycardia

Study details	Key efficacy findings	Key safety findings	Comments
McElhinney DB (2011)[4] **Case series** USA Multi-centre study (Melody® valve IDE trial) Recruitment period: 2007-10 Study population: Patients with dysfunctional RVOT conduits or bioprosthetic pulmonary valves. Primary implant indication was for conduit regurgitation (53%), conduit stenosis (27%) or mixed (20%). n=**150** Age: median 19 years Sex: 58% males Patient selection criteria: Inclusion; aged 5 years or above, weight more than 30 kg, echocardiographic evidence of RVOT	Number of patients analysed: **142 patients** <table><tr><td></td><td>Pre-implant</td><td>Post-implant</td></tr><tr><td>Peak RVOT gradient (mmHg)</td><td>35 (8-80)</td><td>19 (5-48)</td></tr><tr><td>Mean Doppler RVOT gradient</td><td>35 (8-80)</td><td>19 (5-48)</td></tr></table>Data reported as median (range) **Freedom from RVOT reintervention** (at 27 months): 86% ± 4 Freedom from RVOT reintervention (at 27 months) after diagnosis with stent fracture : 49% ± 10 **Freedom from diagnosis of stent fractures** <table><tr><td>Timing (months)</td><td>Type I stent fracture (%)</td><td>Type II stent fracture (%)</td></tr><tr><td>14</td><td>77 ±4</td><td>Not reported</td></tr><tr><td>27</td><td>68± 5</td><td>85 ±4</td></tr><tr><td>39</td><td>60± 9</td><td>74 ±11</td></tr></table> **Freedom from any stent fracture** <table><tr><td>Variable</td><td>HR (95% CI)</td><td>p- value</td></tr><tr><td>Valve implant within any intact prestent or bioprosthetic valve</td><td>0.14 (0.07 to 0.30)</td><td><0.001</td></tr></table>	**Stent fractures** Stent fractures were diagnosed in 39 patients <table><tr><td>n</td><td>timing</td></tr><tr><td>11</td><td>3 months</td></tr><tr><td>15</td><td>6 months</td></tr><tr><td>6</td><td>1 year</td></tr><tr><td>6</td><td>2 years</td></tr><tr><td>1</td><td>3 years</td></tr></table>33 patients were initially diagnosed with type I stent fracture. 17 patients were diagnosed with type II stent fracture (6 at initial identification and 11 patients progressed from type I to type II). **Other complications** **Death** 1 patient died of unknown causes (2 years after the procedure). There was no evidence of valve dysfunction or stent fracture 'at the most recent evaluation'. **Explantation** 2 patients underwent valve explant 5 and 21 months after the procedure.	• Patients included in this study are part of the Melody® valve IDE trial and there is overlap of patients included in McElhinney (2010)[3] included in table 2. **Follow-up issues**: • 8 patients lost to follow-up. Reasons: death (n=1), valve explantation (n=2), and missing scheduled visits (n=3), unclear (n=2). **Study design issues**: • Stent fracture classified as type I (fracture ≥1 strut without loss of stent integrity), type II (fracture with loss of stent integrity) and type III (separation of fragments or embolisation).Stent fractures assessed with chest radiograms 2-month, 1 –year and

Abbreviations used: APV, absent pulmonary valve syndrome; BMS, bare metal stent; CT, computed tomography; IQR, interquartile range; MRI, magnetic resonance imaging; NR, not reported; PA, pulmonary artery; PI, pulmonary insufficiency; PPVI, percutaneous pulmonary valve implantation; PVR, pulmonary valve replacement; RV, right ventricle; RVOT right ventricular outflow tract; SD, standard error; SEM, standard error of the mean; TGA, transposition of the great arteries; ToF, Tetralogy of Fallot; TTE, transthoracic echocardiography; VSD, ventricular septal defect; VT, ventricular tachycardia

Study details	Key efficacy findings	Key safety findings	Comments
conduit dysfunction. Exclusion; acute endocarditis, major progressive non-cardiac disease Follow-up: median 30 months Conflict of interest/source of funding: Medtronic sponsored and funded the study. All authors declared they act as investigators, consultants and/or proctors for Medtronic.	<table><tr><td>Valve substantially apposed to chest wall</td><td>2.5 (1.2 to 5.0)</td><td>0.01</td></tr><tr><td>Compression of the deployed valve</td><td>2.5 (1.1 to 1.54)</td><td>0.02</td></tr></table> **Freedom from valve dysfunction or reintervention** <table><tr><td></td><td colspan="2">**Freedom from valve dysfunction**</td><td colspan="2">**Freedom from valve reintervention**</td></tr><tr><td>Variable</td><td>HR (95% CI)</td><td>p-value</td><td>HR (95% CI)</td><td>p-value</td></tr><tr><td>Valve implant within any intact present or bioprosthetic valve</td><td>0.20 (0.07 to 0.53)</td><td>0.001</td><td>0.18 (0.06 to 0.57)</td><td>0.004</td></tr><tr><td>Mean RVOT gradient post implant</td><td>1.12 (1.06 to 1.17)</td><td><0.001</td><td>1.07 (1.02 to 1.30)</td><td>0.007</td></tr><tr><td>Compression of the deployed valve</td><td>5.3 (2.0 to 14.1)</td><td>0.001</td><td>6.1 (2.3 to 16.5)</td><td><0.001</td></tr></table>		annual follow-up visits and fluoroscopy at 6 month visit. • For analysis of freedom from intervention patients who underwent conduit explant because of acute procedural complications were not included. • Multivariable Cox regression models built in stepwise manner. Number of variables included was based on the number of events for the outcome and 'no more than 2 or 3' variables were in the final model. **Study population issues**: • Initially patients with contraindication to MRI, patients in whom concomitant transcatheter interventions were indicated and

Abbreviations used: APV, absent pulmonary valve syndrome; BMS, bare metal stent; CT, computed tomography; IQR, interquartile range; MRI, magnetic resonance imaging; NR, not reported; PA, pulmonary artery; PI, pulmonary insufficiency; PPVI, percutaneous pulmonary valve implantation; PVR, pulmonary valve replacement; RV, right ventricle; RVOT right ventricular outflow tract; SD, standard error; SEM, standard error of the mean; TGA, transposition of the great arteries; ToF, Tetralogy of Fallot; TTE, transthoracic echocardiography; VSD, ventricular septal defect; VT, ventricular tachycardia

Study details	Key efficacy findings	Key safety findings	Comments
			patients with a bioprosthetic valve not housed in a circumferential conduit were excluded. • 51% of patients had ToF as the primary cardiac diagnosis. 73% of patients had homografts and 25% had one or more existing conduit stents from previous catheterisation with 8% with existing fractures. **Other issues:** • One study included in table 2 (McElhinney 2010)[3] and one included in appendix A (Zahn 2009) are interim reports of this study • Study noted that there was considerable variation among centres in conduit preparation procedures.

Abbreviations used: APV, absent pulmonary valve syndrome; BMS, bare metal stent; CT, computed tomography; IQR, interquartile range; MRI, magnetic resonance imaging; NR, not reported; PA, pulmonary artery; PI, pulmonary insufficiency; PPVI, percutaneous pulmonary valve implantation; PVR, pulmonary valve replacement; RV, right ventricle; RVOT right ventricular outflow tract; SD, standard error; SEM, standard error of the mean; TGA, transposition of the great arteries; ToF, Tetralogy of Fallot; TTE, transthoracic echocardiography; VSD, ventricular septal defect; VT, ventricular tachycardia

Study details	Key efficacy findings	Key safety findings	Comments
Eicken A (2011)[5] **Case series** Germany Recruitment period: 2006-10 Study population: Patients with RVOT dysfunction. Primary indication was stenosis (35%), regurgitation (18%) or a combination of both (47%). Patients had on average 3 preceding cardiac operations. n=**102** Age: median 22 years Sex: 61% males Patient selection criteria: Patients age >5 years, weight >20kg patients with severe pulmonary regurgitation with evidence of RVOT, supraventricular or ventricular rhythm disturbances were	Number of patients analysed: **102** **Cardiac function** Data reported are median (IQR); + Assessed by MRI	**Complications** **Death** One patient died because of left coronary artery compression which occurred 'hours after the procedure' (patient died 2 weeks following the procedure). **Stent fractures** Incidence of stent fractures was 5% (5/102). Two patients showed fracture of a single stent strut (present on chest X-ray; assessed before discharge). **Atrioventricular block** Complete atrioventricular block occurred in 1 patient during the procedure (after 21 days sinus rhythm recurred without pacemaker implantation). **Endocarditis** One patient developed bacterial endocarditis resulting in removal of the valve surgically and replaced by a homograft valve (6 months after the procedure). Partial occlusion of the origin of the right pulmonary artery after PPVI was reported in 1 patient (treated by recatheterisation).	**Follow-up issues**: • No loss to follow-up reported. **Study design issues**: • Consecutive patients enrolled at 2 centres. **Study population issues**: • Majority of the patients (60%) had undergone surgical correction of a TOF/PA with VSD. 77% of conduits used during previous surgery were homograft conduits. Only 5 patients had a 'native' RVOT without a conduit.

	Preoperative	Postoperative	P value
RV-to-PA systolic gradient (mmHg)	37(29-46)	14 (9-17)	<0.0001
RV end-diastolic volume index+ (mL/m^2)	106 (93-133)	90 (71-108) (before discharge 2 days after the procedure)	<0.001
Peak systolic RVOT gradient (mmHg)	37 (29-46)	14 (19-17)	<0.001
Mean Doppler RVOT gradient (mmHg)	36 (26-44)	15 (12-20)	<0.0001
Pulmonary regurgitation + (%)	16 (5-26)	1 (0-2)	<0.001

Abbreviations used: APV, absent pulmonary valve syndrome; BMS, bare metal stent; CT, computed tomography; IQR, interquartile range; MRI, magnetic resonance imaging; NR, not reported; PA, pulmonary artery; PI, pulmonary insufficiency; PPVI, percutaneous pulmonary valve implantation; PVR, pulmonary valve replacement; RV, right ventricle; RVOT right ventricular outflow tract; SD, standard error; SEM, standard error of the mean; TGA, transposition of the great arteries; ToF, Tetralogy of Fallot; TTE, transthoracic echocardiography; VSD, ventricular septal defect; VT, ventricular tachycardia

Study details	Key efficacy findings	Key safety findings	Comments
included. Exclusion criteria not listed. Technique: Under general anaesthesia or deep sedation, femoral vessel access was achieved. Selective angiogram was undertaken during conduit dilatation using a balloon. A bovine valve (Melody®, Medtronic), integrated into a covered stent was then placed in the conduit Prestenting was done in 94% (97/102) of patients. Follow-up: median 1 year Conflict of interest/source of funding: None	**Exercise testing** Peak oxygen consumption (VO_2max) changed from median 22.4 mlO_2/kg/min to 22.8 mlO_2/kg/min following the procedure. **Repeat catheterisation** 8.8% (9/102) of patients had repeat catheterisations because of significant residual systolic pressure gradient (> 50mmHg). In 8 of these patients a repeat dilatation of the valve was done which resulted in a valve-in-valve procedure in 4 patients (because of fractures in 3 patients).		

Abbreviations used: APV, absent pulmonary valve syndrome; BMS, bare metal stent; CT, computed tomography; IQR, interquartile range; MRI, magnetic resonance imaging; NR, not reported; PA, pulmonary artery; PI, pulmonary insufficiency; PPVI, percutaneous pulmonary valve implantation; PVR, pulmonary valve replacement; RV, right ventricle; RVOT right ventricular outflow tract; SD, standard error; SEM, standard error of the mean; TGA, transposition of the great arteries; ToF, Tetralogy of Fallot; TTE, transthoracic echocardiography; VSD, ventricular septal defect; VT, ventricular tachycardia

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Kenny D (2011)[6]

Case series
Multicentre study
USA and Europe

Recruitment period: 2008-10
Study population: Patients with moderate to severe pulmonary regurgitation with or without stenosis.
Number of previous interventions: open heart surgery: 1.94 (range 1-5)(timing from previous intervention to PPVI not reported).

n=36
Age: mean 30 years
Sex: 57% male

Patient selection criteria: patients with dysfunctional RV-PA conduit, defined as ≥3+ pulmonary</td>
<td>Number of patients analysed: 34
Procedural success
Procedural success was achieved in 97.1% (33/34) of attempts. No cases of acute valve failure reported at 6 months.
Device success
(defined as deployment of the valve to the target area and removal of the delivery catheter and improvement in the regurgitation to mild or less (≤2+) (assessed on echocardiogram)
Device success was achieved in 86.1% (25/36) patients (using intention-to-treat criteria)
Haemodynamic data (during the procedure)
<table>
<tr><th></th><th>Pre-implantation</th><th>Post-implantation</th><th>P value</th></tr>
<tr><td>RV systolic pressure (mmHg)</td><td>55.3 ± 18.2</td><td>42 ±13.2</td><td><0.001</td></tr>
<tr><td>RV diastolic pressure (mmHg)</td><td>10.5± 4.0</td><td>9.2± 4.3</td><td>0.036</td></tr>
<tr><td>RV –PA pressure gradient(mmHg)</td><td>26.8± 18.4</td><td>11.7± 8.0</td><td><0.001</td></tr>
<tr><td>Diastolic PA pressure (mmHg)</td><td>9.3± 3.1</td><td>12.4± 5.5</td><td><0.001</td></tr>
</table>
Data reported as mean± SD</td>
<td>No mortality, stent fractures (assessed using chest radiograph or CT), conduit aneurysm formation or pulmonary embolism were reported at 6 month follow-up.
Complications: 20.5% (n=7/34)
<table>
<tr><th>Complication</th><th>n</th></tr>
<tr><td>Ventricular fibrillation (2 episodes during the procedure)</td><td>n=1 (successfully treated by cardioversion)</td></tr>
<tr><td>Mild pulmonary haemorrhage (during the procedure)</td><td>n=2
(spontaneously resolved without need for blood transfusion in both patients)</td></tr>
<tr><td>Valve migration</td><td>n=3 (treated by surgical removal and transapical delivery of 26 mm valve in 1 patient; surgical removal and surgical PVR in 1 patient; and in 1 patient the valve deployed in the inferior vena cava because of proximal stent migration and patient was treated by a further valve implantation during the same procedure).</td></tr>
<tr><td>Stent migration to right ventricle</td><td>n=1(treated by surgical removal and surgical PVR)</td></tr>
</table></td>
<td>Follow-up issues:
• 2 lost to follow-up (valve deployment not attempted in 2 patients due to inappropriate conduit size)
Study design issues:
• All adverse events adjudicated by an independent committee.
• Severity of pulmonary regurgitation graded from 0 (absent) to 4 (severe).

Study population issues:
• Primary diagnosis was ToF in majority of patients (44%) and 81% had homograft.
Other issues:
• This report is an early result of the COMPASSION trial with follow-up protocol scheduled</td>
</tr>
</table>

Abbreviations used: APV, absent pulmonary valve syndrome; BMS, bare metal stent; CT, computed tomography; IQR, interquartile range; MRI, magnetic resonance imaging; NR, not reported; PA, pulmonary artery; PI, pulmonary insufficiency; PPVI, percutaneous pulmonary valve implantation; PVR, pulmonary valve replacement; RV, right ventricle; RVOT right ventricular outflow tract; SD, standard error; SEM, standard error of the mean; TGA, transposition of the great arteries; ToF, Tetralogy of Fallot; TTE, transthoracic echocardiography; VSD, ventricular septal defect; VT, ventricular tachycardia

Study details	Key efficacy findings	Key safety findings	Comments
regurgitation by TTE or pulmonary regurgitant fraction ≥ 40% by cardiac MRI were included. Exclusion criteria not listed Technique: Under fluoroscopic guidance with patients under general anaesthesia, a bovine valve (Sapien®, Edwards Lifesciences) was delivered over a guidewire and deployed with balloon inflation. Prestenting was performed either in a separate procedure (n=12) or during the implantation procedure (n=24). Patients were given antibiotics before valve implantation. In the protocol, it was recommended heparin was given during the procedure and aspirin given evening before procedure and continued for the	**Cardiac functioning** (assessed with TTE) **Baseline (n=31)** / **Follow-up** / **P value** Conduit peak gradient (mmHg): 41.9 ±26.2 / 19.1 ±13.3 / <0.001 Conduit mean gradient (mmHg): 24.0± 15.0 / 12.0± 8.8 / <0.001 Estimated RV pressure (mmHg): 67.3± 20.6 / 49.3± 11.1 / <0.005 Data reported are mean± SD **Cardiac functioning** (assessed with MRI), **Baseline** / **Follow-up** / **P value** Pulmonary regurgitant fraction (%): 28.6 ±18.0 (n=31) / 3.5 ± 5.4 (n=29) / <0.001 RV end diastolic volume (ml/m^2): 130.9± 62.6 / 86.9± 19.6 / 0.02		up to 5 years. • Eight patients underwent implantation with a 26 mm valve and the remaining with 23 mm valve. • Cardiopulmonary exercise testing performed using a ramp workload protocol

Abbreviations used: APV, absent pulmonary valve syndrome; BMS, bare metal stent; CT, computed tomography; IQR, interquartile range; MRI, magnetic resonance imaging; NR, not reported; PA, pulmonary artery; PI, pulmonary insufficiency; PPVI, percutaneous pulmonary valve implantation; PVR, pulmonary valve replacement; RV, right ventricle; RVOT right ventricular outflow tract; SD, standard error; SEM, standard error of the mean; TGA, transposition of the great arteries; ToF, Tetralogy of Fallot; TTE, transthoracic echocardiography; VSD, ventricular septal defect; VT, ventricular tachycardia

Study details	Key efficacy findings	Key safety findings	Comments
duration of trial. Follow-up: **6 months** Conflict of interest/source of funding: Trial was sponsored and funded by Edwards Lifesciences. Two authors reported receiving grants from the manufacturers and one author was an employee at Edwards Lifesciences during the course of the trial	**Pulmonary regurgitation** (assessed by echocardiography) **Severity of pulmonary regurgitation** / **Baseline (n=31)** (%) / **Follow-up (n=29)** (%) 0 / 3 / 72 1+ / 3 / 14 2+ / 0 / 10 4+ / 94 / 3 **Cardiopulmonary exercise testing** **Baseline** / **Follow-up** / **P value** Peak VO_2 max (ml/kg/min) / 22.1 ±9.4 / 23.1± 8.0 / 0.09 Respiratory quotient at peak exercise / 0.9± 0.1 / 0.9 ±0.2 / 0.23 Study noted majority of patients failed to reach anaerobic threshold and changes in peak oxygen consumption were difficult to interpret. **Reintervention** 1 patient underwent elective placement of a second valve because of conduit-induced distortion of the initial implant. Patient required surgical removal of the 2 valves and		

Abbreviations used: APV, absent pulmonary valve syndrome; BMS, bare metal stent; CT, computed tomography; IQR, interquartile range; MRI, magnetic resonance imaging; NR, not reported; PA, pulmonary artery; PI, pulmonary insufficiency; PPVI, percutaneous pulmonary valve implantation; PVR, pulmonary valve replacement; RV, right ventricle; RVOT right ventricular outflow tract; SD, standard error; SEM, standard error of the mean; TGA, transposition of the great arteries; ToF, Tetralogy of Fallot; TTE, transthoracic echocardiography; VSD, ventricular septal defect; VT, ventricular tachycardia

Study details	Key efficacy findings	Key safety findings	Comments
	placement of a different type of valve (8 months after the initial procedure) **NYHA** NYHA functional class in implanted patients only (n=33)		

NYHA functional class	Baseline (%)	30-day follow-up (%)	6 month follow-up (%)
I	15 (n=5)	73	82 (n=27)
II	52	24	12
III	27	0	3
IV	6	0	0
Unknown	0	3	3

Absolute figures were not reported for all categories at all time points.

Abbreviations used: APV, absent pulmonary valve syndrome; BMS, bare metal stent; CT, computed tomography; IQR, interquartile range; MRI, magnetic resonance imaging; NR, not reported; PA, pulmonary artery; PI, pulmonary insufficiency; PPVI, percutaneous pulmonary valve implantation; PVR, pulmonary valve replacement; RV, right ventricle; RVOT right ventricular outflow tract; SD, standard error; SEM, standard error of the mean; TGA, transposition of the great arteries; ToF, Tetralogy of Fallot; TTE, transthoracic echocardiography; VSD, ventricular septal defect; VT, ventricular tachycardia

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Vezmar M (2010)[7]

Case series
Canada
Recruitment period: 2005-2008
Study population: Patients with chronic RVOT and volume overload undergoing PPVI because of RVOT stenosis (32%), pulmonary regurgitation (7%) or a combination (61%).
Time from last intervention to PPVI : 5.2± 2.8 years
n = 28

Age: median 15 years

Sex: 57% male

Patient selection criteria; included patient meeting clinical criteria on RV systolic pressure, morphological criteria on RVOT</td>
<td>Number of patients analysed: varied depending on the outcomes and time of follow-up.

Cardiac functioning (echocardiographic assessment)
<table>
<tr><th></th><th>Before PPVI</th><th>After PPVI (24 hours) (n=24)</th><th>12 months (n=16)</th><th>36 months (n=3)</th><th>p value*</th></tr>
<tr><td>RV systolic pressure</td><td>78 ± 22</td><td>58 ± 17</td><td>53 ± 12</td><td>54 ± 11</td><td><0.001*</td></tr>
<tr><td>RV-PA gradient</td><td>67 ± 23</td><td>41 ± 16</td><td>32 ± 11</td><td>31± 5</td><td><0.001*</td></tr>
<tr><td>RV diastolic pressure</td><td>11 ±5</td><td>10 ±4 (at catheterisation)</td><td>NR</td><td>NR</td><td><0.04</td></tr>
</table>
Data reported as mean ±SD (units: mmHg)
*It is unclear for which time-point the p-values relate to
Cardiac MRI (n=14) (assessed median 183 days after the procedure)
<table>
<tr><th></th><th>Before PPVI</th><th>After PPVI</th><th>P value</th></tr>
<tr><td>RV end diastolic volume (ml/m^2)</td><td>149 ±49</td><td>114 ±35</td><td>0.005</td></tr>
</table>
</td>
<td>Complications
Acute complications (n=2): 1 balloon rupture during conduit pre-dilation without vessel injury and 1 conduit disruption after balloon dilatation (tear sealed by valve implant).

Local vascular complication (arterial aneurysm) was reported in 1 patient (treated by ultrasound guided compression).

Incidence of stent fractures :
Stent fractures were reported in 10.7% (3/28) of patients (review of digital radiographic images; mean 7.5 months follow-up). One patient (stent fracture noted at 3 months) subsequently underwent elective surgical repair.

Explantation
One patient underwent conduit replacement with bilateral pulmonary arterioplasties (3 months after the initial procedure).</td>
<td>Follow-up issues:
Study reported loss to follow-up and noted cardiac MRI and cardiopulmonary exercise testing could not be obtained for the entire cohort (reasons not reported)
Study design issues:
Degree of pulmonary regurgitation determined qualitatively by colour-flow Doppler and categorised as 0 (none) to 4 (severe).
Timing of follow-up varied for outcomes and did not include all ofthe cohort.
Exercise testing was performed with a ramp protocol.</td>
</tr>
</table>

Abbreviations used: APV, absent pulmonary valve syndrome; BMS, bare metal stent; CT, computed tomography; IQR, interquartile range; MRI, magnetic resonance imaging; NR, not reported; PA, pulmonary artery; PI, pulmonary insufficiency; PPVI, percutaneous pulmonary valve implantation; PVR, pulmonary valve replacement; RV, right ventricle; RVOT right ventricular outflow tract; SD, standard error; SEM, standard error of the mean; TGA, transposition of the great arteries; ToF, Tetralogy of Fallot; TTE, transthoracic echocardiography; VSD, ventricular septal defect; VT, ventricular tachycardia

Study details	Key efficacy findings	Key safety findings	Comments
dimensions, weight >20 kg , with moderate to severe PI accompanied by at least 1 symptom. Exclusion criteria included age <5 years, pregnancy, occluded central veins, active infection or coronary anatomy at risk of compression at the time of implant	<table><tr><td>RV end-systolic volume (ml/m^2)</td><td>85 ±48</td><td>63 ±29</td><td>0.005</td></tr><tr><td>RV ejection fraction (%)</td><td>42 ±15</td><td>46 ±13</td><td>0.43</td></tr><tr><td>Left ventricular ejection fraction (%)</td><td>56± 9</td><td>60± 7</td><td>0.24</td></tr><tr><td>Regurgitation fraction (%)</td><td>24 ±10</td><td>7± 7</td><td><0.0001</td></tr></table> **Improvement in pulmonary regurgitation** (assessed qualitatively by colour-flow Doppler) 68% (19/28) patients had moderate to severe pulmonary regurgitation (≥grade 3) before implant. 80% (n=19) had no detectable pulmonary regurgitation (p<0.001) at 1 month. 62% of patients (absolute figures not reported) had no pulmonary regurgitation, 31% of patients had 'trivial' pulmonary regurgitation (grade 1), and 1 patient had 'moderate' (grade 3) pulmonary regurgitation (at 24 months follow-up).		• A mean RVOT gradient ≥ 40 mmHg was used as a cut-off for pulmonary stenosis; grade 3 or more for pulmonary insufficiency. **Study population issues:** • Majority of the patients (57%) had a variant of ToF with pulmonary atresia.61% of patients had previously implanted pulmonary valved conduit of biological origin.

Abbreviations used: APV, absent pulmonary valve syndrome; BMS, bare metal stent; CT, computed tomography; IQR, interquartile range; MRI, magnetic resonance imaging; NR, not reported; PA, pulmonary artery; PI, pulmonary insufficiency; PPVI, percutaneous pulmonary valve implantation; PVR, pulmonary valve replacement; RV, right ventricle; RVOT right ventricular outflow tract; SD, standard error; SEM, standard error of the mean; TGA, transposition of the great arteries; ToF, Tetralogy of Fallot; TTE, transthoracic echocardiography; VSD, ventricular septal defect; VT, ventricular tachycardia

Study details	Key efficacy findings	Key safety findings	Comments
Technique: All procedures performed under general anaesthesia, using a femoral approach (n=23) or a transjugular approach (n=5). During valve implantation simultaneous balloon inflation in the RVOT was undertaken in patients at risk of coronary compression. Follow-up: median 28 months Conflict of interest/source of funding: Not reported	**Exercise testing (at median 6 month follow-up)** | | **Before PPVI (n=24)** | **After PPVI (n=19)** | **p-value** | | --- | --- | --- | --- | | Peak VO_2 (ml/kg/min) | 24 ±5 | 28± 4 | <0.0001 | | VE/VCO_2 | 39± 5 | 36± 5 | <0.003 | *****The study noted that VE/CO_2 improved and that there was a significant difference. However, a normal level (31 ± 5) was not achieved **Freedom from reoperation or reintervention** Freedom from reoperation was 91% at 12 months and 83% at 24 and 36 months. Freedom from transcatheter intervention was 91% at 12 months and 80% at 24 and 36 months. **Reintervention** Balloon dilatation of the implant was performed in 5 patients (mean 15 months after the initial procedure). None of these patients had stent fractures.		**Other issues**: • Additional procedures undertaken at time of PPVI were RVOT stent (n=7), right pulmonary artery stent dilation (n=2) and inferior cava vein stent dilation (n=1).

Abbreviations used: APV, absent pulmonary valve syndrome; BMS, bare metal stent; CT, computed tomography; IQR, interquartile range; MRI, magnetic resonance imaging; NR, not reported; PA, pulmonary artery; PI, pulmonary insufficiency; PPVI, percutaneous pulmonary valve implantation; PVR, pulmonary valve replacement; RV, right ventricle; RVOT right ventricular outflow tract; SD, standard error; SEM, standard error of the mean; TGA, transposition of the great arteries; ToF, Tetralogy of Fallot; TTE, transthoracic echocardiography; VSD, ventricular septal defect; VT, ventricular tachycardia

Study details

Nordmeyer J (2008)[8]

Case series

UK and France

Recruitment period: 2000-07

Study population: Patients who underwent repeat PPVI for RV hypertension because of RVOT obstruction with early device failure (residual stenosis: n=4; stent fracture: n=9; 'hammock' or 'hammock' like effect: n=7).

Second PPVI performed at mean 16 months following the index procedure.

n=**20** (who underwent repeat PPVI in cohort of 173 patients).

Age: median 18 years

Sex: 65% male

Patient selection criteria: Patients were

Key efficacy findings

Number of patients analysed: **19**

Echocardiographic outcomes

	Pre second PPVI	**Post second PPVI**	**Latest follow-up (mean 11 months)**	**p-value***
RVOT gradient	82.5 ±4.9	41.2 ± 3.1	34.2 ±2.4	<0.001
RV systolic pressure	91.1 ±5.7	53.6 ±3.9	48.0± 1.6	<0.001
RV-to systemic pressure ratio	0.52 ±0.02	0.45 ±0.02	NR	<0.05
Pulmonary regurgitation (on a scale of 0 to 4)	0 (0-2)	0(0-2)	0(0-2)	0.40

Data reported as mean ±SEM (units mmHg) unless otherwise specified. *p-values reported for pre-second PPVI compared with latest follow-up (or post second PPVI value if data for latest follow-up not available)

In 15/20 there was sustained improvement at latest follow-up when compared with immediate post-procedural results.

Key safety findings

Complications	n
Stent fracture (assessed with chest x-ray)	2 patients (resulted in recurrent RVOT obstruction and treated by third PPVI at 3 years)
Endocarditis	1 patient (valve was explanted at 6 months)
Recurrent RVOT obstruction (because of severe external compression of the RVOT conduit)	1 patient (explantation of valve at 1 year)

Comments

Follow-up issues:

- 1 patient who underwent repeat PPVI at the same session as index procedure was excluded from analysis.

Study design issues:

- Retrospective review
- Non-blinded follow-up assessment
- Degree of pulmonary regurgitation (assessed using colour-flow mapping of the RVOT and branch pulmonary arteries): 0= absent to 4=sever pulmonary regurgitation.
- Probability of freedom from re-intervention obtained using Kaplan-Meier

Abbreviations used: APV, absent pulmonary valve syndrome; BMS, bare metal stent; CT, computed tomography; IQR, interquartile range; MRI, magnetic resonance imaging; NR, not reported; PA, pulmonary artery; PI, pulmonary insufficiency; PPVI, percutaneous pulmonary valve implantation; PVR, pulmonary valve replacement; RV, right ventricle; RVOT right ventricular outflow tract; SD, standard error; SEM, standard error of the mean; TGA, transposition of the great arteries; ToF, Tetralogy of Fallot; TTE, transthoracic echocardiography; VSD, ventricular septal defect; VT, ventricular tachycardia

Study details	Key efficacy findings	Key safety findings	Comments
considered for second PPVI if they re-met the indication criteria for the index PPVI Technique: Under general anaesthesia access was obtained by the right femoral vein in most patients. A stent-mounted valve was deployed in the RVOT and the position confirmed by angiography. Follow-up: **11 months (latest follow-up)** Conflict of interest/source of funding: Authors received honoraria from Medtronic, Inc.	**Cardiopulmonary exercise testing (n=14)** Peak oxygen uptake increased significantly following placement of a second device: 26.4 ± 1.6 to 29.3 ±1.9 ml/kg/min ($p<0.05$) **Freedom from reintervention** Freedom from reintervention (at 2 years) was higher after second PPVI (89.4%) when compared with the index procedure (20.0%) ($p<0.001$) **Reintervention** Balloon dilatation of the implant was performed in 5 patients (mean 15 months after the initial procedure). None of these patients had stent fractures.		plots. **Study population issues**: • There may be some overlap of patients with one study (Lurz 2008)[2] included in table 2. • No patient in this series required a second PPVI for recurrent pulmonary regurgitation. The index procedure was performed for significant pulmonary regurgitation in 45% (9/20) of patients. **Other issues:** • Prestenting with bare-metal stents was used more in second PPVI (12/20) compared with index procedure (2/20).

Abbreviations used: APV, absent pulmonary valve syndrome; BMS, bare metal stent; CT, computed tomography; IQR, interquartile range; MRI, magnetic resonance imaging; NR, not reported; PA, pulmonary artery; PI, pulmonary insufficiency; PPVI, percutaneous pulmonary valve implantation; PVR, pulmonary valve replacement; RV, right ventricle; RVOT right ventricular outflow tract; SD, standard error; SEM, standard error of the mean; TGA, transposition of the great arteries; ToF, Tetralogy of Fallot; TTE, transthoracic echocardiography; VSD, ventricular septal defect; VT, ventricular tachycardia			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Register (UK Central Cardiac Audit Database)[9] (Cunningham D: personal communication 2012) UK (8 centres) Years: 2004–11 Study population: patients treated by PPVI n=175 Age: mean 27 years Sex: 61% male		Complications • Acute cardiac arrest n=1 • Late cardiac arrest n=3 • Late endocarditis n=1	• Unpublished data from the Congenital Heart Disease section of CCAD. • It is unclear how long these patients were followed up for.

Efficacy

Procedural success

In a case series of 36 patients the valve was successfully implanted in 97% (33/34) of patients[6].

Freedom from reoperation

In a case series of 155 patients, 93% (standard deviation [SD] 2%), 86% (SD 3%), 84% (SD 4%) and 70% (SD 13%) of patients did not need to have further surgery and 95% (SD 2%), 87% (SD 3%), 73% (SD 6%), and 73% (SD 6%) did not need any further transcatheter reintervention at 10, 30, 50, and 70 months respectively (absolute figures not reported)[2].

In a case series of 102 patients, a repeat dilatation of the valve was done in 8% (8/102) of patients because of significant residual systolic pressure gradient, which resulted in a valve-in-valve procedure in 4 patients (timing not reported)[5].

Cardiac function

A non-randomised comparative study of 108 patients, 54 treated by PPVI and 54 treated by pre-stenting followed by PPVI, reported a significant decrease in mean right ventricular systolic pressure from 57 mmHg (SD 16) to 42 mmHg (SD 11) for patients treated by PPVI alone (n=52) ($p<0.0001$) and from 65 mmHg (SD 23) to 41 mmHg (SD 13) in patients treated by pre-stenting followed by PPVI (n=54) ($p<0.0001$) at 1-year follow-up. The mean change was significantly different between the groups ($p=0.02$)[1].

In the case series of 155 patients, there was a significant reduction in mean right ventricular systolic pressure from 63 mmHg (SD 18) to 45 mmHg (SD 13) ($p<0.001$) and RVOT gradient from 37 mmHg (SD 20) to 17 mmHg (SD 10) after the procedure ($p<0.001$)[2].

In the case series of 102 patients, the median end-diastolic right ventricular volume index assessed by magnetic resonance imaging (MRI) decreased from 106 ml/m^2 (range 93 to 133 ml/m^2) at baseline to 90 ml/m^2 (71 to 108 ml/m^2) before discharge 2 days after the procedure ($p<0.001$)[5].

In a case series of 28 patients, pulmonary regurgitation fraction significantly decreased from 24% to 7% in 14 patients ($p<0.0001$) at median 183 days after the procedure. In the case series of 102 patients, pulmonary regurgitation (assessed by MRI) significantly decreased from a median of 16% (range 5 to 26%) to 1% (range 0 to 2%) after the procedure[7].

A case series of 20 patients who underwent repeat PPVI for RVOT obstruction reported a significant decrease in right ventricle to systemic pressure ratio after

the second PPVI compared with the index PPVI. The mean value decreased from 0.52 to 0.45 at 11-month follow-up ($p<0.05$)[8].

Functional capacity

In the case series of 36 patients, the percentage of patients with NYHA functional status of I increased from 15% (5/33) at baseline to 82% (27/33) at 6-month follow-up. Patients with NYHA functional status IV decreased from 6% at baseline to 0% at 6-month follow-up[6].

Exercise capacity

In the case series of 28 patients, cardiopulmonary exercise testing showed that the oxygen uptake (peak VO_2) improved from 24 ml/kg/minute (SD 5) before treatment with PPVI (n=24) to 28 ml/kg/minute (SD 4) at median 6-month follow-up (n=19) ($p<0.0001$). In the case series of 36 patients, the oxygen uptake (peak VO_2 max) changed from 22 ml/kg/minute (SD 9) to 23 ml/kg/minute (SD 8) at 6-month follow-up; this change was not significant ($p=0.09$)[7].

In the case series of 20 patients who underwent a second PPVI, there was a significant improvement in peak oxygen uptake from 26 ml/kg/min to 29 ml/kg/min (n=14; $p<0.05$) at 11 month follow-up[8].

Safety

Mortality

Death was reported in 4% (2/54) of patients treated by PPVI alone and in 4% (2/54) of patients treated by pre-stenting followed by PPVI in the non-randomised comparative study of 108 patients (1 death was within 30 days because of pulmonary oedema). In patients treated by PPVI alone, 1 patient died after a chest infection 2 months after the procedure and 1 patient with pulmonary hypertension died after 'presumed' arrhythmia 24 months after the procedure. In patients treated by pre-stenting followed by PPVI, 1 patient died because of pulmonary oedema 1 day after the procedure [as noted above] and 1 patient died because of 'presumed' arrhythmia 8 months after the procedure [1].

Death (within 30 days) was reported in less than 1% of patients (1/136) in the case series of 136 patients. The patient had coronary artery dissection and intracranial haemorrhage[3].

Stent fractures

Stent fractures were reported in 29% (15/52) of patients treated by PPVI alone and in 17% (9/52) of patients treated by pre-stenting followed by PPVI at 1-year follow-up in the non-randomised comparative study of 108 patients[1]. Stent fractures occurred in 21% (absolute figures not reported) of patients in a case series of 155 patients. Nine patients had required reintervention (further details not reported) by median 28-month follow-up[2].

Explantation

The valve had to be removed in 4% (2/54) of patients treated by PPVI alone in the non-randomised comparative study of 108 patients. This was because of RVOT pseudoaneurysm in 1 patient (at 16 months) and endocarditis in 1 patient (at 19 months). In the same study the device had to be removed in 4% (2/54) of patients treated by pre-stenting followed by PPVI. This was caused by the RVOT becoming obstructed because of a fractured stent and subsequent endocarditis at 5 months in 1 patient and at 15 months in 1 patient. Patients were treated by surgical RVOT revision[1].

Atrioventricular block

Complete atrioventricular block occurred in 1 patient during the procedure in the case series of 102 patients; the patient's heart rate reverted to sinus rhythm after 21 days[5].

Valve migration

Valve migration was reported in 9% (3/34) of patients in the case series of 36 patients. Two patients were treated by surgical pulmonary valve replacement. Valve migration during the procedure was reported in 1 patient who was treated by a further implantation during the same procedure (no further details reported)[6].

Conduit rupture

Conduit rupture/tear (no further details) was reported in 2 patients in a case series of 136 patients at 6-month follow-up. One patient was treated by replacement conduit and the other by covered stent placement[4].

Endocarditis

Bacterial endocarditis was reported in 1 patient in the case series of 102 patients. The valve was surgically removed and replaced by a homograft valve (6 months after the procedure)[5]. Endocarditis was reported in 1 patient in the case series of 20 patients and the valve was explanted at 6 months[8].

Functional capacity

In a case series of 136 patients, functional status in 5 patients declined from NYHA class I before the procedure to NYHA class II at 2-year follow-up. In 3 patients this was associated with stent fracture and recurrent RVOT obstruction[3].

Validity and generalisability of the studies

- The technology has developed over time and different valve systems were used in the studies reported in table 2.

- The patients were heterogeneous in terms of underlying anatomical abnormalities and in the number of interventions undertaken before PPVI. Most of the studies included in table 2 related to patients who had already received homografts or bioprosthetic valves.
- The study populations included both adults and children.
- Diverse outcome measures were used to assess the efficacy of the intervention and only 1 paper stated criteria for success.
- Most patients received the valve via femoral venous access although the jugular vein was used for access in some patients.
- Associated anticoagulant and/or antiplatelet treatment regime is not specified in all of the included studies.
- The evidence base is limited by a lack of long-term data.

Existing assessments of this procedure

Two published assessments were identified at the time of the literature search. The Australia and New Zealand Horizon Scanning Network's report (ANZHSN 2009)[9] on PPVI published in November 2009 concluded that the 'limited evidence from a single case series study suggests that PPVI is associated with low mortality rates and is relatively safe with encouraging short term results'. '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'. An evaluation by the French Health Authority[10] noted that 'study results showed the benefit of the device. Nevertheless, it highlights the need for longer term follow-up (>2 years)'. They also noted that the procedure adds substantial added clinical value compared with conduit replacement surgery.

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B gives details of the recommendations made in each piece of guidance listed.

Interventional procedures

Radiofrequency valvotomy for pulmonary atresia. NICE interventional procedure guidance 95 (2004). Available from http://guidance.nice.org.uk/IPG95

Balloon dilatation of pulmonary valve stenosis. NICE interventional procedure guidance 67 (2004). Available from http://guidance.nice.org.uk/IPG67

Balloon dilatation with or without stenting for pulmonary artery or non-valvar right ventricular outflow tract obstruction in children. NICE interventional procedure guidance 76 (2004). Available from http://guidance.nice.org.uk/IPG76

Specialist Advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and does not represent the view of the society.

Dr Stephen Brecker, British Cardiovascular Intervention Society and Dr David Anderson, Dr Tony Salmon and Dr John Thomson, British Congenital Cardiac Association

- One Specialist Adviser has performed this procedure regularly, 1 has performed this procedure at least once and 2 Specialist Advisers have never performed this procedure.
- All Specialist Advisers considered the procedure was an established practice and no longer new. Two noted that less than 10% of specialists engage in this area of work and 1 noted that 10 to 50% specialists engage in this area of work.
- The Specialist Advisers listed the following key efficacy outcomes: freedom from reintervention, reduced pulmonary incompetence, lower right heart pressure, improved right ventricular function, elimination of regurgitation and gradient, avoiding a sternotomy incision and cardiopulmonary bypass, and shorter recovery time with less risk of infection and bleeding.
- The Specialist Advisers listed the following theoretical adverse events: damage to blood vessels used to introduce the device, perforation of the heart, embolisation of the device, transient rhythm disturbance, infection, bleeding from the cannulation site, stent fracture, death, conduit rupture, residual stenosis, valve dysfunction (related to stent fracture), embolisation, vascular perforation, arrhythmia, malpositioning of the valves, valve embolisation, stent migration and embolisation, pulmonary artery dissection and rupture, emergency cardiac surgery, early or late endocarditis, and late pulmonary regurgitation.

- Three Specialist Advisers considered anecdotal adverse events and those reported in the literature to be the same as those listed as theoretical adverse events.
- In relation to efficacy of the procedure, 1 Specialist Adviser stated that there are uncertainties about long-term outcomes. Another Specialist Adviser noted that the main issue is the durability of the valve and that when a valve is placed within an existing valve it will be inevitably smaller and perhaps obstructive to a degree.
- One Specialist Adviser noted that there is some uncertainty about patient selection.
- Two Specialist Advisers stated that, if shown to be safe and efficacious, the procedure is likely to be carried out in at least 10 hospitals in the UK and one stated fewer than 10 specialist centres in the UK. One Specialist Adviser stated that it would be carried out in more than 10 specialist centres.
- In terms of numbers of patients eligible for treatment and use of resources, 2 Specialist Advisers stated that this procedure would have a moderate impact and 2 stated that this procedure would have a minor impact on the NHS.

Patient Commentators' opinions

NICE's Patient and Public Involvement Programme sent 6 questionnaires to 1 trust for distribution to patients who had the procedure (or their carers). NICE received no completed questionnaires.

Issues for consideration by IPAC

- The devices used in this procedure may use tissue from animals. These valves may not be acceptable for patients in some religious groups.
- Ongoing trials:
  - Melody® Transcatheter Pulmonary Valve Post-Approval Study. Location: USA; Estimated enrolment: 100; Study start date: July 2010; Estimated study completion date: July 2016.

- Congenital Multicenter Trial of Pulmonic Valve Regurgitation Studying the SAPIEN Interventional THV (COMPASSION trial); Location: USA; Estimated enrolment: 70; study start date: April 2008; estimated completion date: March 2018.

References

1. Nordmeyer J, Lurz P, Khambadkone Set al.(2011) Pre-stenting with a bare metal stent before percutaneous pulmonary valve implantation: acute and 1-year outcomes. Heart Jan;97(2):118-23
2. Lurz P, Coats L, Khambadkone S et al. (2008) Percutaneous pulmonary valve implantation: impact of evolving technology and learning curve on clinical outcome. Circulation Apr 15;117(15):1964-72
3. McElhinney DB, Hellenbrand WE, Zahn EM et al. (2010) Short- and medium-term outcomes after transcatheter pulmonary valve placement in the expanded multicenter US melody valve trial. Circulation Aug 3;122(5):507-16
4. McElhinney DB, Cheatham JP, Jones TK, et al. (2011) Stent fracture, valve dysfunction, and right ventricular outflow tract reintervention after transcatheter pulmonary valve implantation: Patient-related and procedural risk factors in the US melody valve trial. Circulation: Cardiovascular Interventions 4 (6):602-14
5. Eicken A, Ewert P, Hager A et al (2011) Percutaneous pulmonary valve implantation: Two-centre experience with more than 100 patients. European Heart Journal 32(10):1260-5
6. Kenny D, Hijazi ZM, Kar S. et al. (2011) Percutaneous implantation of the Edwards SAPIEN transcatheter heart valve for conduit failure in the pulmonary position: early phase 1 results from an international multicenter clinical trial. Journal of the American College of Cardiology;58(21):2248-56
7. Vezmar M, Lee K-J, Chaturvedi R et al. (2010) Percutaneous pulmonary valve implantation in the young: 2 year followup JACC: Cardiovascular Interventions 2(4): 440-448
8. Nordmeyer J, Coats L, Lurz P, et al. (2008) Percutaneous pulmonary valve-in-valve implantation: a successful treatment concept for early device failure. European Heart Journal 29(6):810-5
9. Australia and New Zealand Horizon Scanning Network (2009) Horizon scanning technology prioritising summary: Percutaneous pulmonary valve implantation Commonwealth of Australia, Canberra, ACT
10. Haute Autorité de Santé (French Health Authority) (2011) Technical Assessment for the National Committee for the evaluation of Medical devices and health technologies (CNEDiMTS) Melody-25 January 2011 (2720)-Opinion [online] Available from http://www.has-sante.fr [accessed 2 May 2012]

Appendix A: Additional papers on percutaneous pulmonary valve implantation for right ventricular outflow tract dysfunction

The following table outlines the studies that are considered potentially relevant to the overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Asoh K, Walsh M, Hickey E,et al. (2010) Percutaneous pulmonary valve implantation within bioprosthetic valves. European Heart Journal;31(11):1404-9.	N=14 Follow-up= 13 months	Implantation was successful in all. Follow-up echocardiography (mean 12.9 +/- 9.8 months) revealed a further reduction in RVP ($P < 0.001$) and RVOT gradients ($P < 0.001$) and an increase in left ventricular end-diastolic volume ($P= 0.01$) and aortic valve annulus diameters ($P < 0.001$).	Larger studies included in table 2.
Atamanyuk I, Raja SG, and Kostolny M (2011) Bartonella henselae endocarditis of percutaneously implanted pulmonary valve: a case report. The Journal of heart valve disease.20 (1): 94-7	N=1 Follow up= 5 years	Endocarditis (culture-negative) of a percutaneously implanted pulmonary valve, caused by Bartonella henselae five years after implantation in a 15-year-old patient with a repaired truncus arteriosus	Outcome reported in table 2.
Berman, D. P., Burke, R., and Zahn, E. M. (2012) Use of a novel hybrid approach to salvage an attempted transcatheter pulmonary valve implant. Pediatric Cardiology 33 (5): 839-42	N = 1 Follow up = 48 hours	Valve malpositioning during implantation was reported (treated using a surgical approach).	Safety outcome reported in table 2.
Bonhoeffer P, Boudjemline Y, Qureshi SA et al. (2002) Percutaneous insertion of the pulmonary valve. Journal of the American College of Cardiology 39: 1664–9.	N= 8 Follow up= 10 months	Mean peak systolic pressure across the RVOT decreased from 74 mmHg at baseline to 44 mmHg after the procedure (p value not reported).All patients had subjective improvement in their symptoms at 10 months' follow-up.	Larger studies included in table 2.
Bonhoeffer P, Boudjemline Y, Saliba Z et al (2000) Percutaneous	N = 1 Follow up = 1 month	No complications at 1-month follow up; patient was in good physical	Larger studies included in table 2.

replacement of pulmonary valve in a right-ventricle to pulmonary-artery prosthetic conduit with valve dysfunction. Lancet 356: 1403–5.		condition.	
Boone RH, Webb JG, Horlick E, et al. (2010) Transcatheter pulmonary valve implantation using the Edwards SAPIEN transcatheter heart valve. Catheterization & Cardiovascular Interventions Feb 1;75(2):286-94.	N=7 Follow up= 22.5 months	At a maximum follow-up of 3.5 years (median 22.5 months), Doppler peak gradients ranged from 7-36 mmHg, and there was no evidence of late stent fracture or structural valve failure. The SAPIEN THV can be used successfully in the treatment of patients with right ventricle to pulmonary artery homograft failure. The valve is durable to at least 3.5 years without stent fracture or regurgitation.	Larger studies included in table 2.
Boudjemline, Y., Brugada, G., Van-Aerschot, I. et al. (2012) Outcomes and safety of transcatheter pulmonary valve replacement in patients with large patched right ventricular outflow tracts. Archives of cardiovascular diseases 105 (8-9) 404-13	N= 13 Follow up= range 5 – 42 months	No stent migration or valve displacement during the procedure or after follow-up. There was no significant pulmonary regurgitation. 'Significant' paraprosthetic leak (no further details) was reported in patient (to be treated by repeat dilatation of the valve).	Larger studies included in table 2.
Butcher CJ, Plymen CM, Walker F. (2010) A novel and unique treatment of right ventricular inflow obstruction in a patient with a Bjork modification of the Fontan palliation before pregnancy. Cardiology in the Young 20(3):337-8.	N=1 Follow up= 6 months	Catheter interventions offer a low-risk option for the treatment of haemodynamic residua and innovative use of new technologies such as the pulmonary stent valve presents a novel, safe, and effective treatment for such conduit problems.	Larger studies included in table 2.
Clur SA, Baan Jr J, Lurz P (2007) Percutaneous implantation of a pulmonary valve: an illustrative case Netherlands Heart Journal. 15(1):27-30	N=1 Follow up= not reported	Mild residual pulmonary regurgitation was reported.	Larger studies included in table 2.
Coats L, Tsang V, Khambadkone S et al. (2005) The potential impact of percutaneous pulmonary valve stent	n = 35 FU = 4 months	Procedure was completed successfully in 95% of attempts.	Same patients reported in Khambadkone (2005). Larger studies included in table 2.

implantation on right ventricular outflow tract re-intervention. European Journal of Cardio-Thoracic Surgery 27 (4): 536–43.		Pressure gradient across the RVOT decreased significantly. Operative complications occurred in 9% of patients.	
Coats L, Khambadkone S, Derrick Get al. (2006) Physiological and clinical consequences of relief of right ventricular outflow tract obstruction late after repair of congenital heart defects. Circulation 113(17):2037-44.	N=19 Follow up = 50 days	PPVI reduced RVOT gradient (51.4 to 21.7 mmHg, p<0.001) and right ventricular systolic pressure (72.8 to 47.3 mmHg, p<0.001) at catheterization. Symptoms and aerobic (25.7 to 28.9 mL.kg(-1).min(-1), P=0.002) and anaerobic (14.4 to 16.2 mL.kg(-1).min(-1), P=0.002) exercise capacity improved.	Larger studies included in table 2.
Demkow M, Ruzyllo W, Biernacka EK, et al. (2011) Transcatheter implantation of the biological Sapien Edwards valve in the pulmonary position – First experiences. Postepy w Kardiologii Interwencyjnej 7 (2) (pp 111-115), (2):111-5.	N=2 Follow up=3 days after the procedure	The valves were implanted successfully without periprocedural complications.	Larger studies included in table 2.
Feinstein JA, Kim N, Mohan RV et al. (2006) Percutaneous pulmonary valve placement in a 10-month-old patient using a hand crafted stent-mounted porcine valve. Catheterization & Cardiovascular Interventions 67: 644–9.	N=1 Follow up=1 year	Echocardiography on the first postoperative day showed only mild pulmonary regurgitation. Right ventricular diameter decreased from 25 mm at baseline to 19 mm 1 day after surgery.	Larger studies included in table 2.
Garay F, Webb J and Hijazi ZM. (2006) Percutaneous replacement of pulmonary valve using the Edwards-Cribier percutaneous heart valve: first report in a human patient. Catheterization & Cardiovascular Interventions 67: 659–62.	N=1 Follow up=1 month	Haemodynamic measurement immediately following the procedure revealing a 16 mmHg gradient across the RVOT, and a right ventricle to systemic pressure ration of 49%. The patient had less shortness of breath at 1-month's follow-up.	Larger studies included in table 2.
Guccione P, Milanesi O, Hijazi ZM et al. (2012)Transcatheter pulmonary valve implantation in native	N=1 Follow up= 9 months	No complications occurred during or after the procedure. . At 9 months, patient's exercise tolerance had	Larger studies included in table 2.

pulmonary outflow tract using the Edwards SAPIEN™ transcatheter heart valve. European Journal of Cardio-Thoracic Surgery y41(5):1192-4.		improved considerably, right ventricle function significantly improved and pulmonary regurgitation was 'trivial'.	
Guccione P, Gagliardi MG Calcagni G et al (2009) Percutaneous implantation of pulmonary valves for treatment of right ventricular outflow tract dysfunction: a single-centre experience. Paediatrics and Child Health. 19 (Suppl 2): S116-9	N= 6 Follow up= 11 months	Right ventricular systolic pressure and right ventricular outflow tract gradient decreased respectively from 61 to 40 mmHg and 37 to 20 mmHg. Follow-up ranged from-to 16 (mean 11) months. All patients were free from reoperation, and valvular competence has been well maintained. One patient experienced recurrence of the obstruction, which was successfully treated with transcatheter balloon dilatation 9 months after the implant.	Larger studies included in table 2.
Haas NA (2012) Percutaneous implantation of the Edwards SAPIEN™ pulmonic valve: initial results in the first 22 patients Clinical Research in Cardiology DOI: 10.1007/s00392-012-0503-8	N = 22 Follow up = mean 6 months	There was a significant decrease in the RV-systolic pressure from 69.7 m Hg to 40.9 mmHg ($p<0.05$). There was a substantial reduction in pulmonary regurgitation from before the procedure (mild, n=2; moderate n=0; severe (n=11) to after the procedure (none/trivial n=20; mild n=1). Major complications reported were dislodgement of the valve, valve became wedged in the inferior vena cava and transient cerebral plexus palsy (no further details).	Larger studies included in table 2.
Hofbeck M, Kretschamar O, Sieverding L (2011) Bilateral percutaneous pulmonary valve implantation in dual conduits from the subpulmonary ventricle to the pulmonary arteries European Hart Journal. 32: 2907	N=1 Follow up = not reported	Angiography following the procedure showed a competence of both pulmonary valves with substantial improvement of flow to both pulmonary arteries.	
Khambadkone S, Coats L, Taylor A et al. (2005) Percutaneous	N=59 Follow up=10 months	In 28 patients there was a significant reduction in pulmonary regurgitation	Larger studies included in table 2.

pulmonary valve implantation in humans: results in 59 consecutive patients. Circulation 112: 1189–97.		fraction on cardiovascular MRI from 21 ± 13% at baseline to 3 ± 4% at 6 days' follow-up ($p < 0.001$). There was no significant change in LVEF from baseline (63%) to 6 days' follow-up (64%) ($p < 0.45$). There were no deaths.	
Kostolny M, Tsang V, Nordmeyer J. (2008) Rescue surgery following percutaneous pulmonary valve implantation. European Journal of Cardio-thoracic Surgery. 33: 607-12	N= 152 Follow-up= mean 25 months	Six patients required emergency surgery and 1 patient sustained a mild neurological impairment.	Safety outcome reported in table 2.
Lauten, A., Hoyme, M., and Figulla, H. R. (2012) Severe pulmonary regurgitation after tetralogy-of-Fallot repair: transcatheter treatment with the Edwards SAPIEN XT heart valve. Heart 98 (8) 623-4	N = 22 Follow up = mean 6 months	Residual regurgitation was confirmed after valve deployment. Functional improvement from NYHA class IV to class II-III was reported at 'early follow-up'.	Larger studies included in table 2.
Lurz P, Nordmeyer J, Muthurangu V, Khambadkone S, Derrick G, Yates R, et al. Comparison of bare metal stenting and percutaneous pulmonary valve implantation for treatment of right ventricular outflow tract obstruction: use of an x-ray/magnetic resonance hybrid laboratory for acute physiological assessment. Circulation 2009 Jun 16;119(23):2995-3001.	N= 14 Follow up= unclear	BMS significantly reduced the ratio of right ventricular to systemic pressure (0.75+/-0.17% versus 0.41+/-0.14%; P<0.001) with no further change after PPVI (0.42+/-0.11; P=1.0). However, BMS resulted in free pulmonary regurgitation (21.3+/-10.7% versus 41.4+/-7.5%; P<0.001), which was nearly abolished after PPVI (3.6+/-5.6%; P<0.001)	Larger studies included in table 2.
Lurz P, Nordmeyer J, Giardini A et al. (2011) Early versus late functional outcome after successful percutaneous pulmonary valve implantation: are the acute effects of altered right ventricular loading all we can expect? Journal of American College of Cardiology	N= 65 Follow up= 12 months	There was a significant decrease in right ventricle end-diastolic volume early after PPVI in both subgroups of patients (pre-procedural predominant pulmonary stenosis [PS] [n=35] or predominant pulmonary regurgitation [PR]). Right ventricle ejection fraction improved early only in	Larger studies included in table 2.

857(6):724-31		the PS group (51 ± 11% vs. 58 ± 11% and 51 ± 12% vs. 50 ± 11%, p<0.001 for PS, p=0.13 for PR).	
MacDonald ST, Carminati M, Butera G (2011) Percutaneous implantation of an Edwards SAPIEN valve in a failing pulmonary bioprosthesis in palliated Tetralogy of Fallot European Heart Journal 32(12): 1534	N= 1 Follow up= not reported	A valve in valve approach allowed treatment of the right ventricular outflow tract without the risk associated with further sternotomy and a reduced hospital stay.	Larger studies included in table 2.
Momenah TS, El OR, Al NK et al (2009). Extended application of percutaneous pulmonary valve implantation. Journal of the American College of Cardiology 19;53(20):1859-63.	N=13 Follow up= 4 months	. All patients were discharged within 2 days after the procedure without complications. After a mean of 4 months follow-up all patients were alive and well. Transthoracic echocardiography showed competent pulmonary valve. Chest X-ray showed no stent migration or fracture.	Larger studies with longer follow-up included in table 2.
Nordmeyer-J Khambadkone, S, Coats L et al (2007) Risk stratification, systematic classification, and anticipatory management strategies for stent fracture after percutaneous pulmonary valve implantation. Circulation115(11):1392-7.	N=123 Follow up=13 months	26 (21.1%) developed stent fracture 0 to 843 days after PPVI (stent fracture-free survival at 1 year, 85.1%; at 2 years, 74.5%; and at 3 years, 69.2%). Stent fracture was classified as type I: no loss of stent integrity (n =17); type II: loss of integrity with restenosis on echocardiography (n =8); and type III: separation of fragments or embolization (n=1).	Safety outcome reported in table 2.
Nordmeyer J, Lurz P, Tsang VT et al. (2009) Effective transcatheter valve implantation after pulmonary homograft failure: a new perspective on the Ross operation. Journal of Thoracic & Cardiovascular Surgery 138(1):84-8.	N= 12 Follow up=19 months	After restoration of right ventricular outflow tract function, indexed right ventricular end-diastolic volume decreased (91 +/- 13 to 78 +/- 12 mL x beat(-1) x m(-2), P < .01) and maximal cardiopulmonary exercise performance improved (peak oxygen consumption 25.4 +/- 2.3 to 30.8 +/- 3.0 mL x kg(-1) x min(-1), P < .01). During follow-up (18.8 +/- 4.6 months), there was 1 device explantation	Larger studies included in table 2.

		(restenosis).	
Palma G, Giordano V, Russolillo V et al. (2011) Percutaneous pulmonary valve implantation after endocarditis of Contegra® valved conduit: a case report. Thoracic and Cardiovascular Surgeon. 59(2): 123-5	N=1 Follow up- 1 year	Endocarditis of the conduit was reported in the patient at 1 year follow-up.	Larger studies included in table 2.
Patel M, Iserin L, Bonnet D et al. (2012) Atypical malignant late infective endocarditis of Melody valve. Journal of Thoracic & Cardiovascular Surgery 143 (4) e32-5	N= 4 Follow up = 3 months to 8 years	All patients with infective endocarditis. 2 patients died (1 of multiorgan failure; 1 of RV failure and ventricular fibrillation). 1 patient treated by antibiotics and 1 patient treated by surgical revision.	Safety outcome reported in table 2.
Pretoroius V, Jones A, Taylor D et al. (2008)Percutaneous valved stent repair of a failed homograft: implications for the Ross procedure. Canadian Journal of Cardiology. 24 :e54	N=1 Follow up= unclear	The valve was successfully implanted, the procedure was well-tolerated and the symptoms resolved.	Larger studies included in table 2.
Rodés-Cabau J, Houde C, Perron J et al. (2007) Delayed improvement in valve hemodynamic performance after percutaneous pulmonary valve implantation. Annals of Thoracic Surgery. 85:1787-8	N=1 Follow up= 3 months	At the end of the procedure the right systolic ventricular pressure was 56 mmHg. Absence of pulmonary regurgitation was shown day after the procedure. Major improvement in haemodynamic function was reported 3 months after the procedure.	Larger studies included in table 2.
Ruf B, Eicken B, Hess J (2010) Transient complete atrioventricular block after percutaneous pulmonary valve implantation. Cardiology in the Young. 20: 704-6	N=1 Follow up= 27 days	Complete atrioventricular block was reported during the implantation and spontaneously reverted to a stable sinus rhythm after 3 weeks.	Safety outcome reported in table 2.

Schievano S, Taylor A, Capelli C et al. (2010) First-in-man implantation of a novel percutaneous valve: a new approach to medical device development EuroIntervention .5:745-50	N=1 Follow up=10 months	Following successful implantation, there were no stent fractures, no pulmonary incompetence. Trivial para-device leak was reported at 6 months. Patient described marked symptomatic improvement.	Larger studies included in table 2.
Vida VL, Speggiorin S, Maschietto N et al. (2010) Surgical re-utilization of a pulmonary valve graft after failed percutaneous treatment Journal of Heart Valve Disease 19 (2): 260-2	N=1 Follow up=10 days	The valve dislodged immediately after implantation. The patient required emergency surgical intervention.	Larger studies included in table 2.
Webb JG, Wood DA, Ye J, et al. (2010) Transcatheter valve-in-valve implantation for failed bioprosthetic heart valves. Circulation 121(16):1848-57	N= 24 Follow up= median 135 days	Valve-in-valve implantations were performed in 24 high-risk patients. Failed valves were aortic (n=10), mitral (n=7), pulmonary (n=6), or tricuspid (n=1) bioprostheses. Implantation was successful with immediate restoration of satisfactory valve function in all but 1 patient. No patient had more than mild regurgitation after implantation. No patients died during the procedure. Thirty-day mortality was 4.2%. Mortality was related primarily to learning-curve issues early in this high-risk experience.	Larger studies included in table 2.
Zahn EM, Hellenbrand WE, Lock JE, McElhinney DB. Implantation of the melody transcatheter pulmonary valve in patients with a dysfunctional right ventricular outflow tract conduit early results from the u.s. Clinical trial. Journal of the American College of Cardiology 2009 Oct 27;54(18):1722-9.	N=34 Follow up= 6 months	Peak systolic conduit gradient fell acutely from 37.2 +/- 16.3 mmHg to 17.3 +/- 7.3 mmHg, and no patient had more than mild PR. There were no deaths or further device explants. At 6-month follow-up, conduit Doppler mean gradient was 22.4 +/- 8.1 mmHg, and PR fraction by magnetic resonance imaging was significantly improved (3.3 +/- 3.6% vs. 27.6 +/- 13.3%, $p < 0.0001$). Stent fracture occurred in 8 of 29	This is an interim report of a study (McElhinney 2010) included in table 2.

		implants; 3 of these were treated with a second Melody valve for recurrent stenosis later in follow-up	

Appendix B: Related NICE guidance for percutaneous pulmonary valve implantation for right ventricular outflow tract dysfunction

Guidance	Recommendations
Interventional procedures	**Balloon dilatation of pulmonary valve stenosis. NICE interventional procedure guidance 67 (2004)** 1.1 Current evidence on the safety and efficacy of balloon dilatation of pulmonary valve stenosis appears adequate to support the use of this procedure, provided that the normal arrangements are in place for consent, audit and clinical governance. 1.2 Balloon dilatation of pulmonary valve stenosis should only be performed in a specialist unit where paediatric cardiac surgery is available. 1.3 The Department of Health runs the UK Central Cardiac Audit Database (UKCCAD) and clinicians are encouraged to enter all patients undergoing paediatric cardiovascular interventions onto this database **Balloon dilatation with or without stenting for pulmonary artery or non-valvar right ventricular outflow tract obstruction in children. NICE interventional procedure guidance 76 (2004).** 1.1 Current evidence on the safety and efficacy of balloon dilatation with or without stenting for pulmonary artery or non-valvar right ventricular outflow tract obstruction in children appears adequate to support the use of this procedure, provided that the normal arrangements are in place for consent, audit and clinical governance. 1.2 The procedure should only be undertaken in specialist paediatric cardiology units. 1.3 The Department of Health runs the UK

	Central Cardiac Audit Database (UKCCAD) and clinicians are encouraged to enter all patients into this database. **Radiofrequency valvotomy for pulmonary atresia. NICE interventional procedure guidance 95 (2004)** 1.1 Current evidence on the safety and efficacy of radiofrequency valvotomy for pulmonary atresia with intact interventricular septum is limited due to the rarity of the condition, but appears adequate to support the use of the procedure for the treatment of seriously ill neonates, provided that normal arrangements are in place for consent, audit and clinical governance. 1.2 Radiofrequency valvotomy for pulmonary atresia with intact interventricular septum should be performed in carefully selected patients in specialist centres with paediatric cardiac surgery facilities. 1.3 The Department of Health runs the UK Central Cardiac Audit Database (UKCCAD) and clinicians are encouraged to enter all patients onto this database.

Appendix C: Literature search for percutaneous pulmonary valve implantation for right ventricular outflow tract dysfunction

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	25/09/2012	Issue 9 of 12, Sept 2012
Database of Abstracts of Reviews of Effects – DARE (CRD website)	25/09/2012	n/a
HTA database (CRD website)	25/09/2012	n/a
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	25/09/2012	Issue 9 of 12, Sept 2012
MEDLINE (Ovid)	25/09/2012	1946 to September Week 2 2012
MEDLINE In-Process (Ovid)	25/09/2012	September 24, 2012
EMBASE (Ovid)	25/09/2012	1974 to 2012 Week 38
CINAHL (NLH Search 2.0 or EBSCOhost)	25/09/2012	1981 to present
JournalTOCS	25/09/2012	n/a

Trial sources searched on

- Current Controlled Trials *meta*Register of Controlled Trials – *m*RCT
- Clinicaltrials.gov
- National Institute for Health Research Clinical Research Network Coordinating Centre (NIHR CRN CC) Portfolio Database

Websites searched

- National Institute for Health and Clinical Excellence (NICE)
- Food and Drug Administration (FDA) - MAUDE database
- French Health Authority (FHA)

- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- Conference search
- General internet search

MEDLINE search strategy

1	Heart Valve Diseases/th [Therapy]
2	Ventricular Dysfunction, Right/su [Surgery]
3	Ventricular Outflow Obstruction/su [Surgery]
4	Pulmonary Valve/su [Surgery]
5	Pulmonary Valve Insufficiency/su [Surgery]
6	(right adj3 ventricular adj3 outflow adj3 dysfunction).tw.
7	RVOT.tw.
8	(right adj3 ventricular adj3 outflow adj3 tract adj3 obstruction).tw.
9	RVOTO.tw.
10	(pulmonary adj3 valve adj3 stenosis).tw.
11	Pulmonary Valve Stenosis/
12	(valvular adj3 pulmonary adj3 stenosis).tw.
13	or/1-12
14	percutaneous*.tw.
15	non-surgical*.tw.
16	14 or 15
17	implant*.tw.
18	replace*.tw.

19 17 or 18

20 ((pulmonary or cardiac) adj3 valve).tw.

21 16 and 19 and 20

22 (percutaneous adj3 pulmonary adj3 valve adj3 implantation).tw.

23 PPVI.tw.

24 (percutaneous adj3 valve adj3 replacement).tw.

25 PVR.tw.

26 Heart Valve Prosthesis Implantation/

27 (transcatheter adj3 valve adj3 replacement).tw.

28 Surgical Procedures, Minimally Invasive/

29 (transcatheter adj3 right adj3 ventricular adj3 outflow adj3 tract adj3 intervention).tw.

30 (pulmonary adj3 valve adj3 (replace* or repair* or reconstruct*)).tw.

31 (pulmonary adj3 balloon adj3 (valvuloplas* or dilat*)).tw.

32 (pulmonary adj3 stent adj3 implant*).tw.

33 (melody or sapien or ensemble).tw.

34 "valve in valve".tw.

35 ((valve* or prosthetic* or prostheses) adj2 (fail* or dysfunction* or repeat* or replace*)).tw.

36 (edwards adj1 sapien).tw.

37 (minimal* adj3 invasive adj3 reoperat*).tw.

38 (transcatheter adj1 valve*).tw.

39 or/21-33

40 13 and 39

41 limit 40 to ed=20110101-20120531

42	or/34-38
43	13 and 42
44	41 or 43
45	limit 44 to english language