보건학석사학위논문

Clinical outcomes after percutaneous pulmonary valve implantation − Systematic review and Meta-analysis

경피적 폐동맥판 치환술 임상결과에 대한 체계적 문헌고찰과 메타분석

2014년 8월

서울대학교 대학원

보건학과 보건학전공

유 지 선

Abstract

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Percutaneous pulmonary valve implantation had been used for over ten years. This study was aimed to analyze clinical outcomes after percutaneous pulmonary valve implant by systematic review and meta-analysis of preexisting published studies. **Method** Literature search was performed on April 2014 via PubMed and Cochrane database using NECA guideline. Out of 599 studies 10 published articles since 2005 were eligible to be included in this study. Meta-analysis was performed using RevMan. **Result** Significant efficacy was shown via pooled immediate hemodynamics, MRI, regurgitation outcomes. RV systolic pressure was significantly decreased (mean difference: 20.03mmHg, 95%: 17.95, 12.11). RV diastolic pressure was decreased (mean difference: 1.69mmHg, 95%: 0.94, 2.26). RV-PA gradient was reduced (mean difference: 18.96, 95%: 15.94, 21.99). End-diastolic RV volume was significantly reduced (mean difference: 26.92, 95%: 16.06, 37.77). **Conclusion** This study shows clinically significant improvement in safety and efficacy percutaneous pulmonary valve implantation.

Keywords : percutaneous pulmonary valve implantation, transcatheter pulmonary valve implantation, systematic review, meta-analysis
Student Number **: 2011-23867**

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I. INTRODUCTION

Congenital heart defects, including right ventricular outflow tract (RVOT) dysfunction, are severe conditions requiring multiple surgical repairs throughout a lifetime.[1] The typical symptom of RVOT dysfunction is cyanosis, which is blue coloration on skin due to lack of oxygen saturation in the tissue, and it may require interventions within very early in life.[1] Nowadays, with the latest medical technology, RVOT may be diagnosed during pregnancy with ultrasound by obtaining views of the outflow tracts.[1] RVOT dysfunction encompasses pulmonary valve stenosis, pulmonary valve incompetence, or the two combined; specific associated diagnoses are tetralogy of Fallot (ToF), truncus arteriosus (TA), transposition of the great arteries (TGA), and others.[2] Treatment mostly involves surgical repairs to the RVOT structure, and, depending on its severity, clinical outcomes may vary.[3]

RVOT dysfunction requires surgical repair, and if it is untreated the actuarial survival chances decrease significantly.[4] Lifetime interventions of RVOT dysfunction results in increased morbidity and mortality along with high costs; therefore, there is a need to reduce the total number of interventions required, and especially to avoid open heart surgery.[5] The percutaneous pulmonary heart valve was introduced in 2000, and it has been used in limited countries since then.[6] The aim of percutaneous pulmonary heart valve implantation is to restore and maintain pulmonary valve competence without need of an open-chest operation. When the percutaneous pulmonary heart valve was

first developed by Bonhoeffer in 2000, it was a bovine jugular valve sutured inside a balloon expandable platinum iridium stent.[6] Several studies concluded that it successfully restores the pulmonary valve function and has a high success rate with relatively acceptable safety profile.[7]

Pulmonary heart valve implantation has shown to delay the need for open-chest surgery, thus, could reduce the total number of interventions over lifetime according to various research findings.[8] However, there has not yet been research done among large populations to study clinical outcomes, and the quantitative result of safety and effectiveness outcomes using pooled data remain controversial.

II. BACKGROUND

2.1 Right Ventricular Outflow Tract Disease

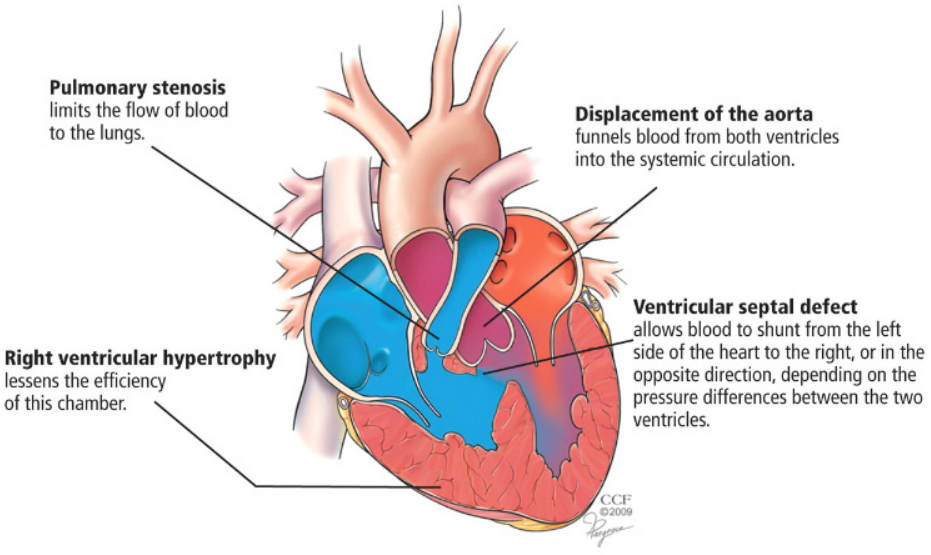
Congenital malformation on right ventricle and pulmonary artery often cause severe symptomatic conditions in early life, which eventually result in the need of series of interventions. Symptoms of RVOT disease include blue baby syndrome, which occurs in babies with cyanotic heart defects caused by insufficient blood flow.[2] In most cases, intervention is required in early stage of life. RVOT usually encompasses pulmonary valve stenosis, pulmonary valve incompetence, or the two combined.[2] Associated diseases are ToF, TA, TGA, and double outlet right ventricle (DORV) diseases.[2] This section intends to provide pathophysiology and epidemiological

background of each associated disease.

Tetralogy of Fallot

ToF is the most commonly occurring RVOT disease, and it is characterized by four major anatomical abnormalities of the heart: pulmonary artery stenosis, ventricular septal defect, deviation of the aortic origin to the right, and right ventricular hypertrophy.[9] Each structural abnormality described in Figure 1.[10] ToF is also the most common congenital heart disease amongst live-born children, and its prevalence rate amongst congenital heart diseases is 9.6%.[11] As with many other congenital diseases, the cause of the disease is unknown; however, commonly, deletion of gen 22q11.2 is detected in ToF patients and it is widely used as a diagnostic tool.[12]

Figure 1. Structure of Tetralolgy of Fallot [10]



Truncus Arteriosus

TA is a congenital heart disease with a single arterial trunk arising from ventricles by means of a single truncal valve. Pulmonary arteries may arise from the common trunk in one of several patterns, which are often used to classify subtypes of TA. Early classification, developed by Collett and Edwards in 1949, classifies TA into four different types (I, II, III, and IV) by structural characterization of the pulmonary trunk.[13] TA is a relatively uncommon congenital heart disease amongst live-born children and its rate of occurrence is about 1.4%.[11] Pathophysiology of TA is typified by cyanosis and systemic ventricular volume overload, which causes a need of right ventricle outflow.

Transposition of Great Arteries

TGA is characterized by the transposition of the great arteries, which are the pulmonary artery and the aorta.[14] As the great arteries are transposed, (i.e., switched), there are two blood circulation systems in the body, which results in a lack of oxygen delivery from the lungs into the whole body. Therefore, as with other RVOT diseases, TGA also results in cyanotic symptoms. The Center for Disease Control and Prevention in Unites States estimates that each year about five out of every 10,000 babies are born with TGA.[15]

Double Outlet Right Ventricle

DORV is a form of ventriculoarterial connection in which both of the great arteries

connect completely or partially to the right ventricle.[14] DORV often presents with other coexisting ventricular anomalies such as mitral stenosis and TGA. DORV with subaortic ventricular septal defect usually yields physiology similar to ToF because the blood from the left ventricle flows to the aorta and blood from the right ventricle flows to the pulmonary artery, and DROV with subpulmonic ventricular septal defect usually yields physiology which is similar to TGA because blood from the left ventricle flows to the pulmonary artery, and blood from the right ventricle flows to the aorta.[14] DORV accounts for about 0.7% of all congenital heart diseases of live-born children.[11]

2.2 Treatment of Right Ventricular Outflow Tract Disease

RVOT dysfunctions discussed above (ToF, TA, TGA, and DORV) have a common symptom of cyanosis in the patient's early years, also known as blue baby syndrome. The symptom of cyanosis occurs due to the lack of continuity between the right ventricle and the pulmonary artery. Severity of symptoms may vary depending on the type of structure abnormality, and it typically presents with pulmonary valve stenosis, pulmonary valve incompetence, or the two combined. Treatment of RVOT dysfunction mostly involves surgical repair, and if it is untreated, the actuarial survival rate is approximately 75% after the first year of life, 60% by four years, 30% by ten years, and 5% by forty years.[4]

Therapeutic Pathway

Depending on the severity of the RVOT disease, a medical decision is made as to whether surgical repair is needed. Most often, RVOT diseases requires surgical repair, which is usually performed in two stages, which are repair and initial revalving.[16] There are different types of surgical repairs and techniques that are used to treat RVOT diseases, and the techniques are chosen depending on the types of dysfunction. Types of surgeries that are commonly performed are Rastelli, Fontan, Ross, Konno, Norwood, among others.

Through primary surgical repair, the most common serious symptom, pulmonary regurgitation, which is, due to the ventricular function affecting the valve function, is generally managed and shows effective outcomes [17]. Moreover, chronic volume overload of the right ventricle leads to ventricular dilatation and impairment of systolic and diastolic function, which in the long term leads to reduced exercise tolerance, arrhythmias, and an increased risk of sudden death. Therefore, after the first surgical repair, in later life, another repair procedure is often required to treat stenotic valved conduits. For stenotic valved conduit, there are several interventional procedures available: balloon angioplasty, percutaneous stent implant, and surgical implant/replacement of the RV−PA conduit. These interventional procedures reduce pressure gradient in RV−PA conduits, but the effect is shown to be short-lived and does not significantly delay the next surgical repair.[18]

RV−PA conduits that are surgically inserted show effective outcomes such as low

perioperative mortality of 1−4% and 10-year survival of 86−95%.[19] However, since it is surgically implanted, there are risks involving cardiopulmonary bypass, infection, and bleeding, and ventricular dysfunction remains, as well as the chronic impact on the myocardium and brain.[20] The RV−PA conduit of freedom from replacement is 68−95% at 5 years, and 0−59% at 10 years.[18]

Therefore, the result of RV−PA conduit follow-up indicates that the need of repair or replacement increases greatly after 10 years of the first conduit procedure; on the other hand, the new currently available prosthetic conduits' functional life expectancy is limited. Thus, as previously discussed, patients with RV-PA conduit would eventually go under a series of operations in their lifetime in order to replace degenerated conduit.

Although Neyt et al. found uncertainty of timing of operation and PPVI indication in later life, they illustrated the timeline of ToF repair in patients for whom early complete repair is not feasible, as shown in Table 1.[16] As the table shows, after initial revalving for the replacement of conduit, PPVI may be appropriate for all, and the age and number of repairs in later life may vary between patients.[16]

Table 1. Timeline of patients with Tetralogy of Fallot in whom early complete repair is not feasible [16]

Repair	Initial revalving	Replacement of conduit (redo)	Redo	Redo
		stenting PPV?[a]		
Age 0–8 months	Age 10–20 years	Age 20–30 years	?	?
Surgical repair of obstructive lesions of the RVOT early in life can be life-saving, but creates pulmonary valve incompetence	Later on, patients need the placement of a (homograft) valved conduit	The lifespan of homografts is much shorter than that of the patients receiving them, thereby making future surgical reintervention(s) unavoidable		

[a]PPV? indicates conditions where percutaneous pulmonary valve (PPV) insertion may be appropriate. Ages may vary widely between patients.
RVOT, right ventricular outflow tract.

Patients with congenital cardiac defects involving the right ventricle and pulmonary artery face multiple re-operations over a lifetime; therefore, there is a need for valve repair or replacement performed with minimally- or less-invasive techniques. The term "less invasive" implies that the patient spends less time in the operating room, acute care unit, and rehabilitation. "Minimally invasive" also implies less discomfort and less impairment of the patient's and the caregiver's daily activities. Early intervention could restore RV function.

The percutaneous pulmonary valve implantation is intended to relieve conduit stenosis without inducing regurgitation, to restore and maintain pulmonary valve competence with the goal of extending the right ventricle to pulmonary artery conduit life, and

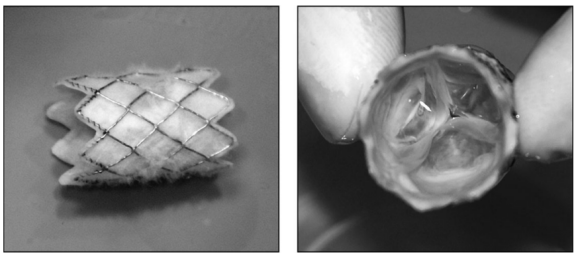
ultimately decrease the number of repeated surgical interventions over a patient's lifetime.

2.3 Percutaneous Pulmonary Valve

Today, there are two types of marketed pulmonary heart valve − Melody™, Medtronic, and Sapien™, Edwards.[21] The Melody valve is a bovine jugular vein valve sutured within a platinum iridum stent and preserved in a proprietary sterilant of glutaraldehyde and alcohol.[21] The Sapien pulmonary transcatheter heart valve is a bovine pericardium valve with a radiopaque, stainless steel balloon-expandable support structure, and a polyethylene terephthalate fabric cuff.[21] The images of the two valves are shown in Figure 2.

Figure 2 Percutaneous Pulmonary Valve [21]

Melody™ valve

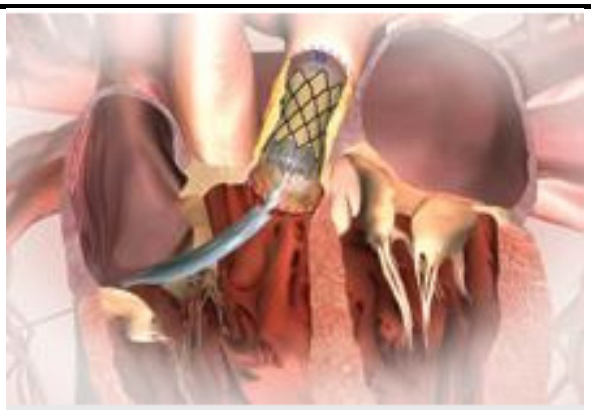


Sapien™ valve

PPVI procedure is very similar to the coronary artery stenting procedure. The patients are usually under general anesthesia, and physicians use fluoroscopy to overlook and monitor the progress of transcatheter procedure. The puncture site used for transcatheter insert is typically the femoral vein, and angiography is used to identify the anatomy of RVOT along with other coronary arteries and veins. The catheter-based delivery system is used to insert the valve, and the delivery system that is used for each percutaneous pulmonary valve is the NovaFlex^{TM} delivery system for Sapien^{TM} and the Ensemble^{TM} delivery system for Melody^{TM}. Prior to inserting the delivery system, the percutaneous pulmonary valve is carefully positioned at the end of the catheter, which has a balloon matching with the diameter of the used valve.

Using fluoroscopy, physicians then position the valve at the targeted site of RVOT, then inflate the balloon to expand the percutaneous pulmonary valve at the target valve. The Melody^{TM} transcatheter pulmonary valve deploying using the Ensemble^{TM} delivery catheter is shown in Figure 3.[22] Then, the balloon is deflated and guidewire is removed, leaving the new valve in place. Depending on the physician's preference, sometimes additional stent is used first to provide solid surface where the valve can be fixed easily, which may decrease the risk of future stent fracture.[3]

Figure 3 Melody transcatheter pulmonary valve deployment using the Ensemble™ delivery catheter [22]



2.4 Epidemiology and target population for PPV

Congenital heart disease prevalence rates may vary among different demographic groups; therefore, in this section, epidemiology for Western and Korean PPV target populations will be discussed separately.

Epidemiology of Western Population

In European countries, the prevalence of congenital heart disease at birth is reported as 0.8%, indicating that, yearly, about 58,640 children are born with a significant heart defect.[2] In 40% of cases, no treatment is needed, whereas in the remaining 60%, surgery or catheter interventions are indicated,[2] which means that about 23,500 children receive surgery or intervention yearly. The prevalences of different congenital cardiac anomalies at birth are depicted in Table 2.

Table 2 Prevalence at birth of specified congenital heart defects in Europe (%) [2]

Ventricular septal defect	42
Atrial septal defect	9
Aortic stenosis	8
Pulmonary stenosis	6
Ductus arteriosus persistens	5
Coarctatio aortae	5
Transposition of great arteries	5
Atrioventricular septal defect	4
Tetralogie of Fallot	3
Hypoplastic left heart	3
Other	10
Total	100

Epidemiology of Korean population

Although Korea has an easily accessible data set provided by te Health Insurance Review and Assessment Service, incidence or prevalence rates for different types of congenital heart disease populations was impossible to calculate because Korean Standard statistical classification does not specify the different types of CHD. Therefore, as with the European population, the publication search was used to research epidemiology of the Korean population. Unfortunately, there was no published study regarding the prevalence at birth; however, there was a study performed on prevalence of specified congenital heart defects in Korea.[23] The research calculated the incidence rate and prevalence rate of all population based on consensus data along with their own survey. Table 2 shows the prevalence for all populations for specified congenital heart defects in Korea.

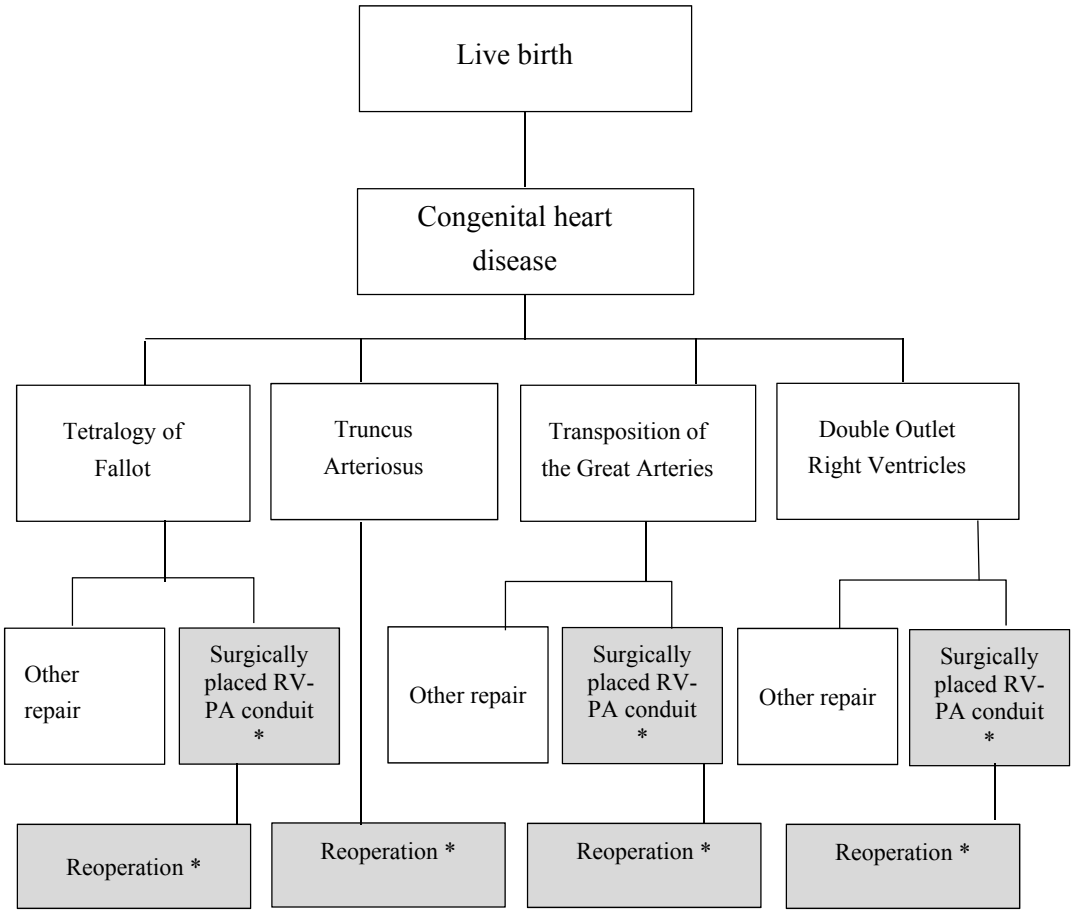
Table 3 All-population prevalence of specified congenital heart defects in Korea (%)

Ventricular septal defect	34.9
Atrial septal defect	18.8
Patent Ductus Arteriosus	10.0
Tetralogie of Fallot	8.4
Pulmonary stenosis	7.0
Coarctatio aortae	2.7
Attrioventricular canal defect	2.1
Ebstein's anomaly	2.0
Mitral valve disease	1.9
Aortic valve disease	1.9
Double outlet right ventricle	1.6
Transposition of great arteries	1.5
Other	8.2
Total	100

Target population of PPVI

By referencing the Medtronic Melody^{TM} humanitarian device submission document, the diagram of the target population is outlined in Figure 4.

Figure 4. Diagram usage of PPVI



* Marked boxes indicate the target population of PPVI

Using the diagram in Figure 4, assumptions concerning the target Korean population calculation can be made. By Congenital Heart Disease Prevalence and Investigation Survey performed in 2008 to 2009 in Korea, prevalences of each PPVI target disease were determined as follow: ToF 8.4%, TA 0.1%, TGA 1.5%, and DORV 1.6%.[23] Out

of those populations, the rates of patients who receive surgical treatments are − ToF 83%, TA 77%, TGA 92%, and DORV 79%. Through the assumption that roughly 15% of RVOT repair involves the RV-PA conduit, the prevalence of each PPVI target disease population is 1.5% of the congenital heart disease population in Korea based on a 2005 census [23]. In other words, 1.5% of congenital heart disease population in Korea could be eligible to receive benefits from PPVI; therefore, safer, more effective PPVI requires further investigation.

III. METHOD

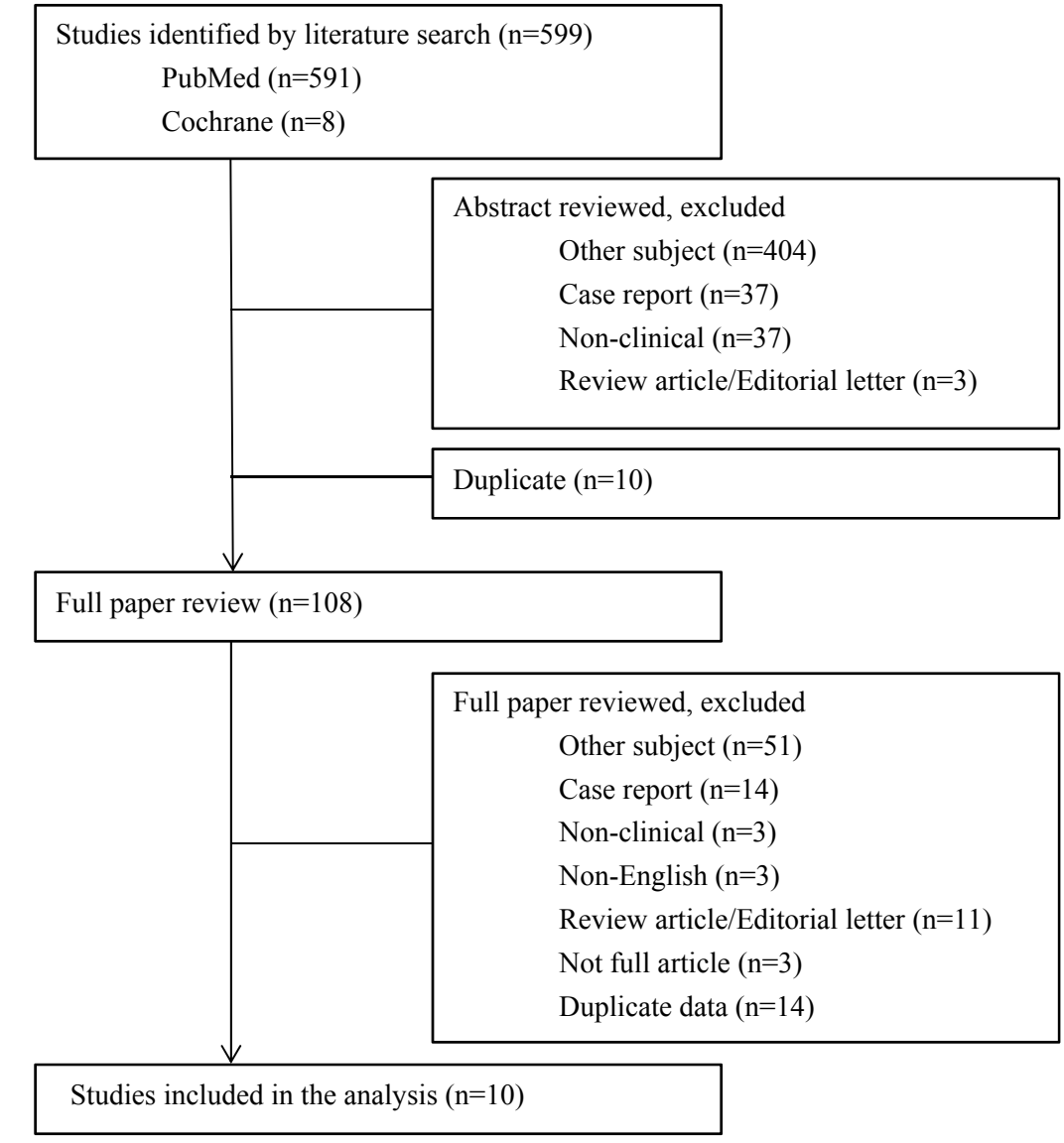
3.1 Search Method

This study was performed as per the National Evidence-based Healthcare Collaborating Agency (NECA) systematic review manual published in 2010. The literature review was performed via two electronic databases: the United States National Library of Medicine (PubMed, at www.ncbi.nlm.nih.gov/pubmed/) and Cochrane Library (at www.thecochranelibrary.com). To eliminate the possible omission of searched literature, broad search terms were used, as follow: "Percutaneous pulmonary valve implantation" and "transcatheter pulmonary valve implantation."

3.2 Inclusion Criteria

The published journal search took place in April 2014. To align the literature search to the objective of this study, the following selection criteria[24] were used − studies with clinical data available for patients who were treated by a regulatory approved percutaneous pulmonary valve − Melody™, or Sapien™ −, studies with complete published article, studies with human subjects only, and studies published in English. Furthermore, studies in the form of case reports were excluded, and if the study was published more than once, the published articles, which contain more complete data, were included. The overview of search method and selection is summarized diagrammatically in Figure 5.

Figure 5 Flow Diagram of Study Search and Selection



3.3 Data Extraction

From eligible studies, baseline characteristics and clinical safety and efficacy outcomes were extracted from each study using Microsoft Word and Excel. Due to data characteristics, safety outcomes were not able to be included in the meta-analysis, while efficacy outcomes were. Commonly, immediate hemodynamic data along with 6 months' follow-up MRI data were mainly described in the selected articles.

A second reviewer also independently searched, in/excluded, and extracted data. These data was compared to the first reviewer's data for accuracy. If there was any disagreement between the two, it was resolved by discussion and agreement.

3.4 Statistical analysis

Endnote software version X7.1 (Thomson Reuters, New York, USA) was used for publication review, and RevMan 5.2 (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark) was used for meta-analysis. The model used for meta-analysis was a fixed-model. Publication bias will be confirmed; funnel plots were constructed to inspect the symmetry visually.

Related Statistical Algorithm in RevMan

PPVI clinical outcomes are in a structure of continuous measurement of pre-procedure and post-procedure groups. Therefore, the following data formation was used for the analysis:[25]

	Group size	Mean response	Standard deviation
Pre-procedure	n_{1i}	m_{1i}	sd_{1i}
Post-procedure	n_{2i}	m_{2i}	sd_{2i}

The mean difference is defined as MDi = m_{1i} - m_{2i}, and standard error is defined as

$$\mathrm{SE}\{MD_i\} = \sqrt{\frac{sd_{1i}^2}{n_{1i}} + \frac{sd_{2i}^2}{n_{2i}}}. \quad (25)$$

In order to pool the intervention effect − continuous PPVI outcomes −, which are all mean differences along with standardized mean differences, RevMan uses the inverse-variance method. The intervention effect is denoted as $\hat{\theta}_i$, whereas the individual effect sizes are weighted according to the reciprocal of their variance:

$$w_i = \frac{1}{\left(\mathrm{SE}\{\hat{\theta}_i\}\right)^2}. \quad (25)$$

Heterogeneity of included studies was tested by using the method similar to the Mantel-Haenzel method. The k represents the number of included studies in the analysis, so k-1 degrees of freedom chi-square distribution was used to test the null hypothesis (no differences of outcomes in pre and post PPVI). I^2 is calculated as

$$I^2 = \max\left\{100\% \times \frac{Q_{IV} - (k-1)}{Q_{IV}}, 0\right\}. \quad (25)$$

IV. RESULTS

The number of searched studies was 599 by using electronic database − PubMed and Cochrane. Abstract review was performed for all searched studies. Among those excluded were 404 non related studies, 37 case report studies, 37 non-clinical studies, three review articles and editorial letters were excluded, and 10 duplicate studies. A full review was performed on 108 studies. Among the 108 fully reviewed studies, 51 non-related studies, 14 case report studies, three non-clinical studies, three non-English studies, 11 review articles and editorial letters, three non-full studies, and 14 studies with duplicate data were excluded.

Thus, ten studies were finally included in this study. The list of included studies is given in Appendix I. In addition, the list of fully reviewed studies along with each exclusion criteria is described in detail in the Appendix II. The total number of included patients is 697 patients and their procedure period was from 2005 to 2012. In all included studies, PPVI was performed for those regulatory approval indications, such as patients with regurgitant prosthetic RVOT conduits with clinical indications for invasive or surgical intervention, and for patients with stenotic prosthetic RVOT conduits where the risk of worsening regurgitation is a relative contraindication to balloon dilation or stenting.[26, 27] Each included study's summary, including study design, method, and outcome, is described in Appendix III.

Although for some studies lacked the information on indication and contraindication of PPVI, for those had the information, the common indication and contraindications for PPVI were as follow: age >5 years, weight >20kg, conduit right ventricular outflow tract 16−18mm or ≤22mm, severe pulmonary regurgitation, progredient RV dilation and reduced RV function, symptomatic patients with declining exercise tolerance, increased RV pressure, a combination of stenosis and regurgitation with RV dysfunction and dilation, and supraventricular or ventricular rhythm disturbances. In addition, the common contraindications of PPVI were active infection, abnormality of coronary artery, and pregnancy.

Table 4 Basic information and patient baseline characteristics of each study

Study	Patients	Age	Gender	Procedure period	Primary diagnosis
Asoh 2009[28]	14	15.4±2.0	F: 7 M: 7	Oct 2005 -Feb 2008	Tetralogy of Fallot (n=4) Pulmonary atresia with VSD (n=3) Truncus arteriosus (n=4) Double outlet right ventricle (n=2) Aortic insufficiency (n=1)
Butera 2013[29]	63	24(11-65)	F:31 M: 32	Oct 2007 − Oct 2010	Tetralogy of Fallot (n=27) Truncus arteriosus (n=5) Aortic valve disease (n=9) Transposition of the great arteris (n=7) Other (n=15)
Eicken 2011[30]	102	21.5 (16.2-30.1)	F: 40 M: 62	Dec 2006 − Jul 2010	Tetralogy of Fallot/pulmonary atresia (n=61) TAC (n=14) transposition of the great arteries (n=9) Aortic stenosis (n=8)

					Others (n=10)
Gillespie 2012[31]	104	26 (3-63)	-	Apr 2007 – Jan 2012	Tetralogy of Fallott (n=77) Truncus arteriosus (n=7) Pulmonary stenosis (n=7) Dextro-transposition of the great arteris (n=4) Aortic stenosis (n=4) Double-outlet right ventricle (n=1) Other (n=4)
Haas 2013[32]	22	21.7 (6-83)	F: 9 M: 13	-	Tetralogy of Fallott (n=11) Pulmonary atresia (n=2) Truncusarteriosus (n=3) TGS/PS-Rastelli (n=1) Ross (n=2) Double outlet right ventricle (n=2) Absent pulmonary valve (n=1)
Kenny 2011[33]	36	30±15.1	F:12, M: 24	Apr 2008 – May 2010	Tetralogy of Fallot (n=16) Ross procedure (n=11) Transposition of the great arteries (n=1) Other (n=8)
Lurz 2008[34]	155	21.2 (7-71)	F: 42% M: 58%	Sep 2000 – Feb 2007	Tetralogy of Fallot (n=94) Double outlet RV (n=9) TGA, VSD, PS (n=14) Ross procedure (n=12) Truncus arteriosus (n=17) Other (n=9)
McElhinney 2010[35]	136	19 (7-53)	-	Jan 2007 – Aug 2009	Tetralogy of Fallot (n=65) (46%) Aortic valve disease after Ross operation (n=28) Transposition of the great arteries (n=15) Truncus arteriosus (n=14) Double-outlet right ventricle (n=8) Valvar pulmonary stenosis (n=3) Other (n=2)
Secchi 2013[36]	27	22±9	F;12 M: 15	Jan 2008 – Jun 2010	Tetralogy of Fallot (n=7) Aortic valve disease (n=7) Transposition of great arteries (n=4) Double outlet right ventricle (n=3) Trucus arteriosus (n=2) Pulmonary atresia (n=2) Pulmonary stenosis (n=2)

Vezmar 2010[37]	28	14.9 (10.9 - 19)	F: 12 M: 16	Oct 2005 – Dec 2008	Pulmonary Atresia with Ventricular Seaptal Defect (n=9) Tetralogy of Fallot (n=7) Paroxysmal Atrial Tachycardia (n=5) Double outlet right ventricle(n=2) Aortic insufficiency (n=2) Transposition of great arteries with pulmonary stenosis (n=2) Other (n=1)

4.1 Clinical Outcome

Immediate Hemodynamic Results

Most studies included outcomes of immediate hemodynamic result, and in total there were 10 studies included.[28, 30-35, 37-39] However, due to varying techniques and units of measurement, only those with three or more study data with the same measurement were pooled for meta-analysis, shown in Table 2.

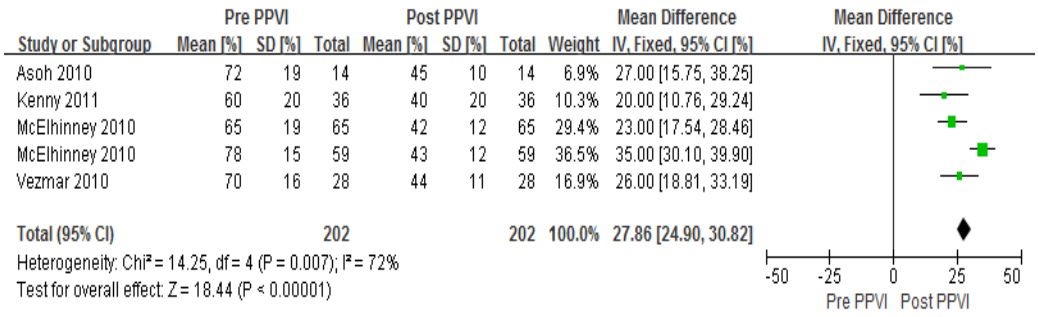
After percutaneous pulmonary valve implantation, ratio of RVP to aortic pressure was significantly decreased (mean difference: 27.86%, 95% CI: 24.90, 30.82). RV systolic pressure was significantly decreased (mean difference: 20.03mmHg, 95% CI: 17.95, 12.11). RV diastolic pressure was decreased (mean difference: 1.69mmHg, 95% CI: 0.94, 2.26). PA systolic pressure was increased (mean difference: -2.61mmHg, 95% CI: -4.35, -0.87). PA diastolic pressure was increased (mean difference: -4.37mmHg, 95% CI: -5.25, -3.49). RV-PA gradient was reduced (mean difference: 18.96, 95% CI: 15.94, 21.99). Aortic systolic pressure was increased (mean difference: -10.51, 95%

CI: -12.89, -8.14).

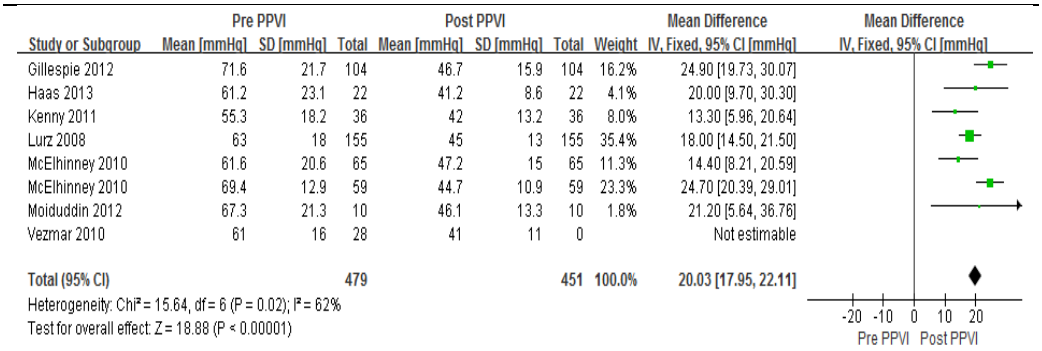
Of these immediate hemodynamic results, significant heterogeneity was found in mean differences of ratios of RVP to aortic pressure, RV systolic pressure, and aortic systolic pressure. The analysis was repeated with a random-effect model, but it showed similar heterogeneity. To evaluate study publication, bias funnel plots were constructed. Due to of the small number of included studies k, and the fact that all included studies are not controlled studies, there was limitation to measure the publication bias. By funnel plot evaluation, it was determined that all tests except ratio of RVP to aortic pressure and RV diastolic pressure are to be 2-sided, meaning there is possibility of publication bias present on RVP to aortic pressure and RV diastolic pressure. In addition, p value showed less than 0.05, which is considered statistically significant.

Table 5 Immediate Hemodynamic Results

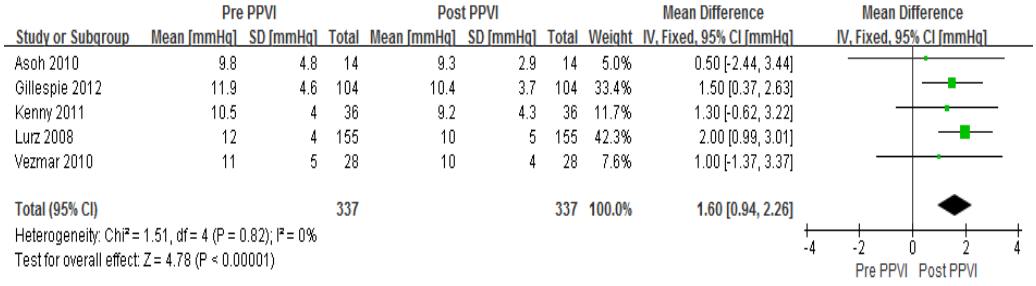
Ratio of RVP to aortic pressure



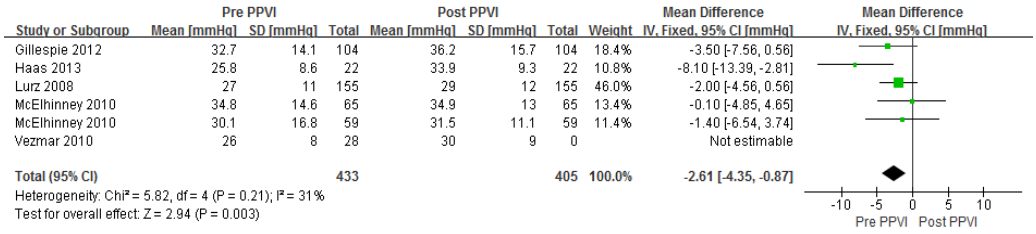
RV systolic pressure



RV diastolic pressure



PA systolic pressure



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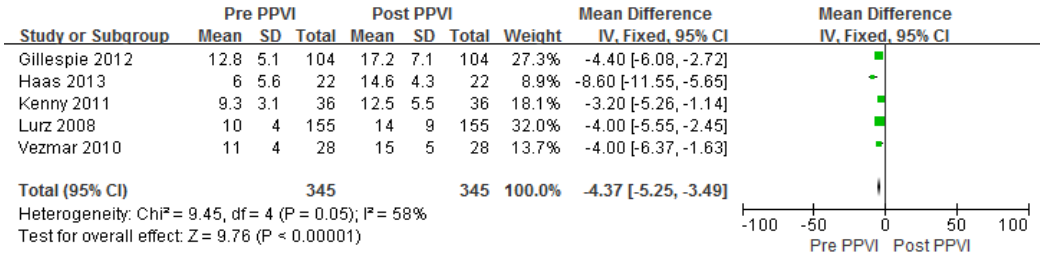
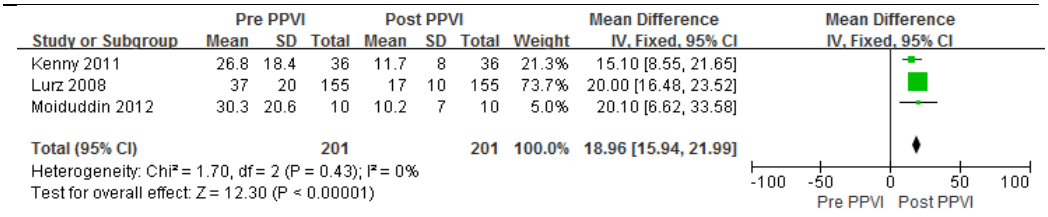
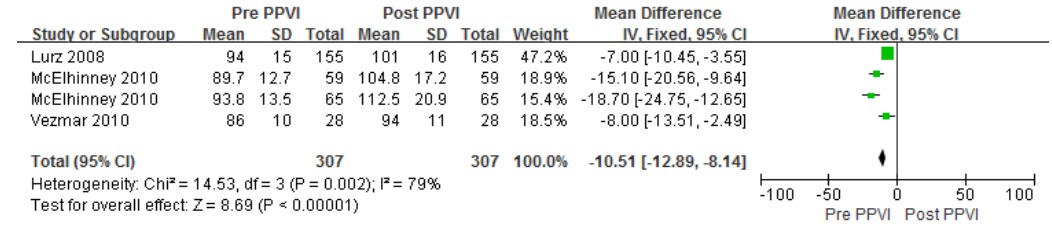


RV-PA gradient



Aortic Systolic Pressure



Mid-term Magnetic Resonance Imaging Results

Out of the 10 studies, mid-term magnetic resonance imaging (MRI) data was available in four studies.[29, 33, 35, 37] Due to different unit and test used in these four, only 6 months' data for End-diastolic RV volume and RV ejection fraction were able to be pooled, as shown in Table 6.

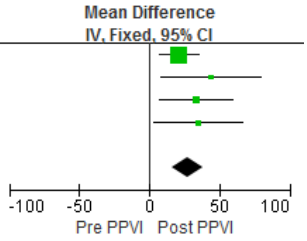
End-diastolic RV volume was significantly reduced (mean difference: 26.92, 95% CI: 16.06, 37.77, p: <0.00001). There was no significant change in RV ejection fraction (mean difference: -1.57, 95% CI: -4.73, 1.60, p: 0.33). There was no shown heterogeneity on these two MRI outcomes. In addition, there was possible publication bias on end-diastolic RV volume, as shown in the funnel plot in Table 6.

Table 6 MRI follow-up data

End-diastolic RV volume

Study or Subgroup	Pre PPVI Mean	SD	Total	Post PPVI Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Butera 2013	90	36	40	69	23	30	61.3%	21.00 [7.14, 34.86]
Kenny 2011	130.9	62.6	13	86.9	19.6	13	9.3%	44.00 [8.34, 79.66]
McElhinney 2010	205.8	90.2	80	172.7	76.3	80	17.6%	33.10 [7.21, 58.99]
Vezmar 2010	149	49	14	114	35	14	11.8%	35.00 [3.46, 66.54]
Total (95% CI)			**147**			**137**	**100.0%**	**26.92 [16.06, 37.77]**

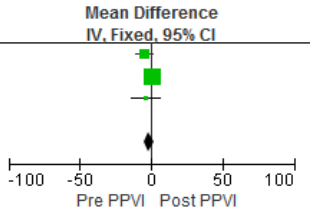
Heterogeneity: Chi² = 2.05, df = 3 (P = 0.56); I² = 0%
Test for overall effect: Z = 4.86 (P < 0.00001)



RV ejection fraction

Study or Subgroup	Pre PPVI Mean	SD	Total	Post PPVI Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Butera 2013	47	12	40	52	12	30	31.1%	-5.00 [-10.68, 0.68]
McElhinney 2010	43.2	14.1	80	42.6	12.3	80	59.6%	0.60 [-3.50, 4.70]
Vezmar 2010	42	15	14	46	13	14	9.3%	-4.00 [-14.40, 6.40]
Total (95% CI)			**134**			**124**	**100.0%**	**-1.57 [-4.73, 1.60]**

Heterogeneity: Chi² = 2.69, df = 2 (P = 0.26); I² = 26%
Test for overall effect: Z = 0.97 (P = 0.33)



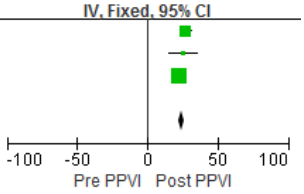
Regurgitation

Out of the 10 studies, three[29, 33, 35] had data on regurgitation fraction. The data was pooled, and Table 7 shows its result. After PPVI, regurgitation fraction was decreased significantly (mean difference: 24.13, 95%CI: 21.64, 26.61, p: <0.00001).

Table 7 Regurgitation Fraction

Study or Subgroup	Pre PPVI Mean	SD	Total	Post PPVI Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Butera 2013	35	10	40	8	7	30	38.8%	27.00 [23.02, 30.98]
Kenny 2011	28.64	18	13	3.47	5.4	13	5.9%	25.17 [14.95, 35.39]
McElhinney 2010	24.8	14.9	80	2.8	3.1	80	55.3%	22.00 [18.67, 25.33]
Total (95% CI)			**133**			**123**	**100.0%**	**24.13 [21.64, 26.61]**

Heterogeneity: Chi² = 3.60, df = 2 (P = 0.17); I² = 44%
Test for overall effect: Z = 19.06 (P < 0.00001)



4.2 Safety Outcome

Death. All the studies show a fairly short follow-up period, which led the mortality rate to be low. There were few death events described in 10 studies, which were reported in three studies.[29, 31, 34] There were three early deaths that occurred due to, respectively, cardiogenic shock, multiorgan failure, and complicated medical history which led to complicated procedure and misplacement of valve.[29, 34] After 6 months, there were three deaths due to respiratory insufficiency, severe liver disease, and progressive heart failure, respectively.[29] At 8 months, there was one sudden death due to arrhythmia. At 35 months, there was one sudden death due to arrhythmia.[34] In addition, with an unknown period, there were two deaths due to postoperative sepsis and hypercarbic respiratory failure.[31]

Freedom from reintervention and reoperation. Freedom from reintervention and reoperation was reported in 4 studies. [28, 30, 34, 37] Asoh describes freedom from reintervention as 13/14 at 1 year, and 12/14 at 2 years. [28] Eicken describes freedom from reintervention as 97±2% at 1 year, and 92±5% at 2 years. [30] Lurz describes freedom from reoperation as 93±2 at 10 month, 86±3 at 30 months, 84±4 at 50 months, and 70±13 at 70 months. [34] Vezmar describes freedom from reoperation as 91% at 1 year, 83% at 2 years, and 83% at 3 years. [37] Vezmar also describes freedom from reintervention as 91% at 1 year, 80% at 2 years, and 80% at 3 years.[37]

Freedom from valve failure. Freedom from valve failure was reported in one study.[29] Butera describes freedom from valve failure as 81.4 ± 9% at 1 year.

Procedural complication Procedural complications occurred in eight studies as follows: six homograft rupture,[34, 35] five major and minor bleeding,[29, 34] three implant failure,[31-33] three vascular surgery requirement,[29] two embolization,[29, 33] two guidewire induced perforation,[35] two stent dislodge,[31, 32] two damage to tricuspid valve,[34] two balloon rupture,[31, 33] two device instability,[34] one femoral artery pseudoneurysm,[28] one ventricular fibrillation,[29] one contrast media leakage,[29] one transjugular access necessary,[31, 32] one Intermittent atrial flutter,[31] one pulmonary hemorrhage,[33] one ventricular fibrillation,[33] one THV mitigation,[33] one Compression of left main artery,[34] one Obstruction,[34] one coronary artery dissection,[35] one tachycardia,[35] one hypercarbia,[35] one femoral vein thrombosis,[35] one balloon angioplasty,[35] one recurrent stenosis,[37] and one conduit stenosis.[37]

Other complications. Other than procedural complications, there were some complications found during each studies' follow-up visits. Ten events of endocarditis were reported in four studies.[29-31, 34] 39 stent fractures were reported in four studies.[29-31, 35] There was one severe compression of left coronary artery,[30] one intermittent atrial flutter,[33] one hemolysis,[34] one pulmonary hypertension,[35] one tricuspid regurgitation,[35] and one sub-dural hemorrhage.[29]

V. DISCUSSION

Effectiveness of Percutaneous Pulmonary Valve Implantation

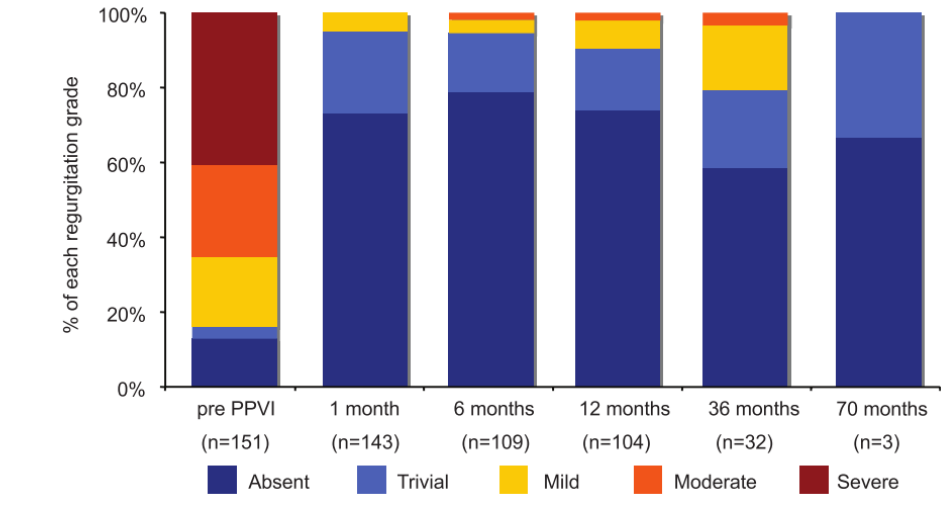
Before the present paper, there had been several published systematic review studies on PPVI[40, 41] but no meta-analyzed data available. Although each outcome were pooled from limited number of studies, analyzed data shown in Table 2 and 3 shows significant improvement on immediate hemodynamic and well-maintained mid-term MRI outcomes. These data show statistically significant differences from pre-implantation and post-implantation of percutaneous pulmonary valves.

However, it remains controversial as to whether this value is comparable to the previous therapy − surgical repair of pulmonary valve. Therefore, the effectiveness of surgical pulmonary valve replacement was searched for reference. There was a meta-analysis study done on surgical pulmonary valve replacement after operative repair of ToF.[42] Although this study only included papers with the patients who had undergone surgical repair of ToF, it pooled data on indexed right ventricle end diastolic volume (mean difference: -63, 95% CI: -72, -55) , RV ejection fraction (mean difference 1, 95% CI: -1, 3), and pulmonary regurgitant fraction (mean difference: -38, 95% CI: -41, -35).[42] Similar to our previous pooled data shown in Table 2 and 3, apart from RV ejection fraction data, right ventricle end diastolic volume and pulmonary regurgitant fraction were reduced significantly. Although quantification of change is different

between PPVI and surgical repair, data comparison between surgical repair and PPVI would not be possible due to statistical limitations.

Rate of regurgitation is one of the greatest tools to measure the effectiveness of PPVI, because it is the most important indication for the use of PPV. Among included studies in this paper, there were three studies with valve regurgitation outcomes. Asoh reports valve regurgitation as absent or mild in 100% of cases at 24 h.[28] Butera and Lurz describes that valve regurgitation was absent or mild in 90% of cases at 6 months.[29] [34] Lurz reports that valve regurgitation was absent or trivial in 80% of cases at 36 months, as shown in Figure 6.[34]

Figure 6. Valvar competence during follow-up assessed on echocardiography - regurgitation



Safety of Percutaneous Pulmonary Valve Implantation

The most common complication found in the follow-up visits was stent fracture. Among the included studies, four studies reported 39 cases of stent fracture.[29-31, 35] Stent fractures are commonly treated with repeated balloon dilatation, stent implantation, or operation. Requirement of another procedure or surgery makes this complication one of the most serious and dangerous. Nordmeyer performed a study on 123 patients who had undergone PPVI,[43] and he reported that 21.1% patients developed stent fracture 0−843 days after PPVI. His study on multivariate analysis of stent fracture risk factors concludes that the risk factors are concluded outflow tract type, calcification along RVOT, and recoil of PPV.[43] The second most common complication was endocarditis, which was reported among four studies.[29-31, 34] It is also a dangerous complication, so aseptic environment is important as well as treating patients with appropriate intravenous antibiotics.

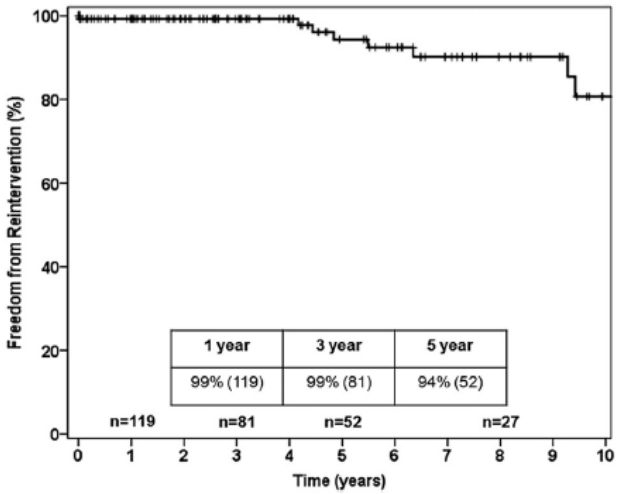
The number of reported death events is low due to the short follow-up period. Among 10 included studies only four studies had described event of death, which summed to be 12 events. There were three early deaths due to cardiogenic shock, multi-organ failure, and complicated medical history, respectively, which led complicated procedure and misplacement of valve.[29, 34] After 6 months, there were three deaths due to respiratory insufficiency, severe liver disease, and progressive heart failure.[29] At 8 months, there was one sudden death due to arrhythmia. At 35 months,[34], there was one sudden death due to arrhythmia.[34] Also, with an unknown period, there were

two deaths due to postoperative sepsis, and hypercarbic respiratory failure, respectively [31]. The relationship of these events to medical device, PPV, or procedure, PPVI, is not clearly reported in the studies.

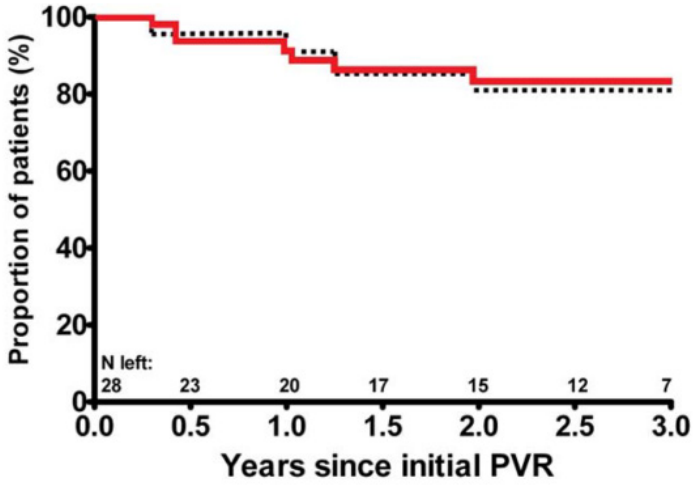
Freedom from reintervention and reoperation is one of the great tools to measure the efficacy and safety of PPVI. There were four studies [28, 30, 34, 37] that analyzed freedom from reintervention and reoperation. As shown in the result session of this paper, all the studies consistently show fairly effective outcomes, and it also shows that the rate slowly decreases with time. Some studies performed on surgical pulmonary valve replacement describe that freedom from PV reintervention is 94% at 5 years, as shown in figure 7, which might seemed to be a better result than PPVI. However, statistical comparison between the two therapies is not possible because due to statistical limitations − no randomized trial, no controlled trial, and included population between the two studies are different.

Figure 7 Freedom from Reintervention

A. Freedom from reintervention for patients eligible for percutaneous intervention who underwent surgical pulmonary valve replacement [44]



B. Freedom from reoperation or reintervention after percutaneous pulmonary valve implantation in young [37]



Cost Effectiveness of Percutaneous Pulmonary Valve Implantation

Although the included studies do not include the data for cost effectiveness analysis, an additional study search was performed to consider cost effectiveness of PPVI.

Cost of Surgical Repair. Prior to discussing the cost effectiveness of PPVI, cost of pulmonary valve surgical repair is to be discussed. While there is a limited number of studies performed on the cost of surgery, although the study performed by Ungerleider only included patients who underwent surgical repair of ToF, it describes the cost that is associated with its surgical repair amongst infants.[45] This study included direct and indirect cost of those who underwent surgical repair of ToF in the United States between 1993 and 1995. The study compared the cost between one-stage repair and two-stage repair of ToF in infants who are younger than 1 year of age, as shown in Table 5. However, his study did not include the cost of care that occurs later in life, such as outpatient visits, cardiac cauterization, and series of echocardiography. The costs reflected here are for a single episode of care that will be repeated several times during the patient's lifetime.[45]

Table 8 Total hospital and health care costs for one-stage vs. two-stage repair of tetralogy of Fallot in infants younger than 1 year of age[45]

Parameter	One-stage primary repair (18 patients)	Two-stage intervention (four patients)
Length hospital of	14.5 ± 11.2 days	43 ± 30.8 days (p=0.003 compared to primary (one-stage) for the complete

stay		repair
Total health care costs	$32,541 ± $15,968	$79,795 ± $40,625 (p=0.001) compared to the group with primary repair for the complete repair

Cost of PPVI − United Kingdom. The study performed in the UK by Raikou compared the analyzed cost of PPVI with the cost of surgical valve replacement in RVOT dysfunction patients.[46] The used model for analysis is a cohort simulation model in the UK, and the mean cost for surgical procedure was £11,610.[46] This cost was mainly attributable to the operative duration time, intensive care, and hospital stay. PPVI was associated with a small increase in treatment management costs of 25 years, but the study was an indication of long-term cost, and did not consider short term cost effectiveness.[46] Based on the assumptions stated above and using a Markov simulation over 25 years, the model resulted in an estimate of mean cost per patient of £5,791 in the absence of PPVI, and in an estimate of mean cost per patient of £8,734 in the presence of PPVI.[46]

Cost of PPVI − United States. Between 2010 and 2011 at a single center in the US, a prospective Markov simulation modeling out to 10 years for 17 patients who received PPVI or surgically placed pulmonary valve.[47] The study compared the cost-effectiveness of PPVI to the standard surgical repair, and the used data included actual

procedural and in-hospital charges, estimation for 5 and 10 year future modeling with appropriate sensitivity analysis. 10-year simulation resulted in surgery costs of $150,437 compared to $128,129 for PPVI.[47] Furthermore, the study concluded that it would need to have very high failure rate to lose its advantage but for now PPVI demonstrated a 6% per year valve failure requiring reintervention. [47] Overall, PPVI was found to have lower initial procedural costs, less time lost from work, and lower length of stay compared to surgery.[47]

Benefits of Percutaneous Pulmonary Valve Implantation

Even though there were some procedural complications reported in the included studies, such as homograft rupture,[34, 35] major and minor bleeding,[29, 34] implant failure,[31-33] and vascular surgery requirement,[29] its utmost benefit of percutaneous pulmonary valve implantation compared to surgical valve implantation is its reduced invasiveness. Advantages of transcatheter procedure over surgery are well described through many studies. Lee et al. report the following advantages: less invasive, low risk of bleeding and infection, and low costs compared with surgical procedure.[40] The most important advantage is providing means of limiting the duration and severity of RV volume and/or pressure overload without increasing the lifetime number of open heart operations, as well as cost reduction.[40]

VI. LIMITATION

Lack of Included Study Number

As previously mentioned, there are several limitations to this study. First, the number of included studies is very limited. The reason for the lack of studies is that the characteristics of RVOT dysfunction have low incidence and prevalence rates amongst live born babies. In addition, PPVI was introduced fairly recently, in 2000, and is not yet marketed around the world, but only to very limited countries such as the U.S. and in Europe.

No Controlled Study to Encounter PPVI Effectiveness

Second, there is no randomized or controlled study available to confirm the effectiveness of PPVI over the previous method (surgical repair). It may be questionable as to how it could be possible considering the fact that PPVI is already a marketed and approved product in many counties. This is due to PPVI's classification, which lead it to be regulated differently. As previously discussed, the incidence rate of PPVI target population is relatively low, which leads it to be classified as a rare disease. Many countries around the world regulate the rare disease differently, and demonstration of the scientific efficacy of the product may not be necessary to gain the product approval, and the below session will address each of the regulations that waive the scientific efficacy requirement of the product submission for the approval.

United States. U.S. Food and Drug Administration (FDA) states the following in the 21 CFR 814.3 − "humanitarian use device" (HUD) means a medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year.

In order to be categorized as a HUD, a humanitarian device exemption (HDE) application needs to be submitted and be approved by FDA. CFR Sections 514 and 515 also illustrate the approval application steps for HUD. The HDE submission document is similar to the premarket approval application, which includes technical, non-clinical laboratory study, and clinical investigation. The only difference between HUD approval requirement and regular pre-market approval requirement is that under the investigational device exemption clinical investigation information on scientifically valid clinical investigation on medical device effectiveness is waived. However, even though the effectiveness information is not required for HUD approval, ample information on risk and benefit of the device usage and the demonstration of no comparable devices are available. Referencing from the Melody^{TM} HUD submission document, which was the first FDA submission for percutaneous pulmonary valve, scientific assumption of U.S. number of PPVI target population number is 1070 per year and it was, thus, categorized as a HUD.

Europe. The European Union regulates medicines for rare disease differently by

orphan designation. European Medicine Agency's Committee for Medicinal Products (COMP) for human use designates orphan medicine if the following criteria are met: it must be for life-threatening or chronically debilitating conditions; prevalence of the condition must not be more than 5 in 10,000 or generate sufficient returns to justify the investment; and no satisfactory method of diagnosis, prevention, or treatment of the condition concerned can be authorized.[48]

The application needs to be completed as Directive 2001/83/EC states by including the following rationales in each section: quality, biologicals, non-clinical, clinical efficacy and safety, and multidisciplinarity. For specific products, the application requirement can be consulted guided by COMP, and orphan devices offer benefits to the company by incentives such as reduced fees and protection from competition once the product is placed on the market. The European Medicines Agency and US Food and Drug Agency work closely together to minimize the approval timeline and expedite the process by allowing applications for orphan-medicine designations to be submitted in parallel. Recently, Pharmaceuticals and Medical Devices Agency (PMDA) also began this cooperation in 2013.

South Korea. Korea has similar regulations as U.S. Devices to treat rare disease regulated by the "rare medical device designation policy." In order for the medical device to be categorized and approved as rare medical devices, the following criteria needs to be fulfilled: an incidence population of 20,000 or less, indication population

is not enough to show clinical effectiveness, no other alternative product available.

Effect of Learning Curve

Third, the effect of learning curve on safety and efficacy outcomes of PPVI was not encountered. As per research done by Lurz in 2008, safety and efficacy outcomes are greatly affected by the operator's learning curve, and it was proven that there was statistically significance.[34] However, in most published articles that were included in this study, there was a limited amount of information on physicians' experience of PPVI. Therefore, considering physicians' experience in this study was not possible. Moreover, timing of operation of initial surgery as well as PPVI procedure and baseline characteristics of patient may greatly affect the safety and efficacy outcomes according to the study performed by Oosterhof[49]; however, this factor could also not be considered due to lack of information.

VII. CONCLUSION

Meta-analysis and systematic review of 10 published articles since 2005 shows clinically significant improvement in safety and efficacy percutaneous pulmonary valve implantation. However, to conclude more definitive outcome, more studies are required for reliable evidence of efficacy for large populations and long-term analysis, and for comparison with surgical result.

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Appendix I Meta-analysis and Systematic Review Included Studies

Asoh, K., et al., Percutaneous pulmonary valve implantation within bioprosthetic valves. Eur Heart J, 2010. 31(11): p. 1404-9.

Butera, G., et al., Melody transcatheter pulmonary valve implantation. Results from the registry of the Italian Society of Pediatric Cardiology. Catheter Cardiovasc Interv, 2013. 81(2): p. 310-6.

Eicken, A., et al., Percutaneous pulmonary valve implantation: two-centre experience with more than 100 patients. Eur Heart J, 2011. 32(10): p. 1260-5.

Gillespie, M.J., et al., Melody valve implant within failed bioprosthetic valves in the pulmonary position: a multicenter experience. Circ Cardiovasc Interv, 2012. 5(6): p. 862-70.

Haas, N.A., et al., Percutaneous implantation of the Edwards SAPIEN() pulmonic valve: initial results in the first 22 patients. Clin Res Cardiol, 2013. 102(2): p. 119-28.

Kenny, D., et al. 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, 2011. 58, 2248-56 DOI: 10.1016/j.jacc.2011.07.040.

Lurz, P., et al., Percutaneous pulmonary valve implantation: impact of evolving technology and learning curve on clinical outcome. Circulation, 2008. 117(15): p. 1964-72.

McElhinney, D.B., et al., Short- and medium-term outcomes after transcatheter pulmonary valve placement in the expanded multicenter US melody valve trial. Circulation, 2010. 122(5): p. 507-16.

Secchi, F., et al., Cardiac magnetic resonance before and after percutaneous pulmonary valve implantation. Radiol Med, 2013.

Vezmar, M., et al., Percutaneous pulmonary valve implantation in the young 2-year follow-up. JACC Cardiovasc Interv, 2010. 3(4): p. 439-48.

Appendix II List of Full Reviewed Studies

No	Study Information	Exclusion criteria*
1	Asoh, K., et al., Percutaneous pulmonary valve implantation within bioprosthetic valves. Eur Heart J, 2010. 31(11): p. 1404-9.	
2	Azadani, A.N. and E.E. Tseng, Transcatheter valve-in-valve implantation for failing bioprosthetic valves. Future Cardiol, 2010. 6(6): p. 811-31.	1
3	Balzer, D.T., Percutaneous pulmonary valve implantation: fixing the problems and pushing the envelope. Curr Opin Pediatr, 2012. 24(5): p. 565-8.	6
4	Basquin, A., et al., Transcatheter valve insertion in a model of enlarged right ventricular outflow tracts. J Thorac Cardiovasc Surg, 2010. 139(1): p. 198-208.	4
5	Batra, A.S., et al., Cardiopulmonary exercise function among patients undergoing transcatheter pulmonary valve implantation in the US Melody valve investigational trial. Am Heart J, 2012. 163(2): p. 280-7.	9
6	Bauner, K. and R. Kozlik-Feldmann, [Minimally invasive pulmonary valve replacement in pediatric patients: importance of imaging]. Radiologe, 2013. 53(10): p. 880-5.	1
7	Bertels, R.A., N.A. Blom, and M.J. Schalij, Edwards SAPIEN transcatheter heart valve in native pulmonary valve position. Heart, 2010. 96(9): p. 661.	3
8	Bonhoeffer, P., et al., Percutaneous insertion of the pulmonary valve. J Am Coll Cardiol, 2002. 39(10): p. 1664-9.	1
9	Boone, R.H., et al., Transcatheter pulmonary valve implantation using the Edwards SAPIEN transcatheter heart valve. Catheter	3

	Cardiovasc Interv, 2010. 75(2): p. 286-94.	
10	Boshoff, D.E., et al., Off-label use of percutaneous pulmonary valved stents in the right ventricular outflow tract: time to rewrite the label? Catheter Cardiovasc Interv, 2013. 81(6): p. 987-95.	1
11	Boudjemline, Y., et al., [Percutaneous pulmonary valve replacement: towards a modification of the prosthesis]. Arch Mal Coeur Vaiss, 2003. 96(5): p. 461-6.	7
12	Boudjemline, Y. and P. Bonhoeffer, Steps toward percutaneous aortic valve replacement. Circulation, 2002. 105(6): p. 775-8.	1
13	Boudjemline, Y., et al., Outcomes and safety of transcatheter pulmonary valve replacement in patients with large patched right ventricular outflow tracts. Arch Cardiovasc Dis, 2012. 105(8-9): p. 404-13.	1
14	Boudjemline, Y., et al., Impact of right ventricular outflow tract size and substrate on outcomes of percutaneous pulmonary valve implantation. Arch Cardiovasc Dis, 2013. 106(1): p. 19-26.	1
15	Brown, D.W., et al., Reliability and accuracy of echocardiographic right heart evaluation in the U.S. Melody Valve Investigational Trial. J Am Soc Echocardiogr, 2012. 25(4): p. 383-392.e4.	1
16	Buber, J., et al., Bloodstream infections occurring in patients with percutaneously implanted bioprosthetic pulmonary valve: a single-center experience. Circ Cardiovasc Interv, 2013. 6(3): p. 301-10.	1
17	Butera, G., et al., Melody transcatheter pulmonary valve implantation. Results from the registry of the Italian Society of Pediatric Cardiology. Catheter Cardiovasc Interv, 2013. 81(2): p. 310-6.	
18	Cheung, G., et al., Infective endocarditis following percutaneous pulmonary valve replacement: diagnostic challenges and application of intra-cardiac echocardiography. Int J Cardiol, 2013. 169(6): p.	1

	425-9.	
19	Chowdhury, S.M., et al., Early echocardiographic changes after percutaneous implantation of the Edwards SAPIEN transcatheter heart valve in the pulmonary position. Echocardiography, 2013. 30(7): p. 786-93.	9
20	Coats, L., et al., Physiological consequences of percutaneous pulmonary valve implantation: the different behaviour of volume- and pressure-overloaded ventricles. Eur Heart J, 2007. 28(15): p. 1886-93.	1
21	Coats, L., et al., Physiological and clinical consequences of relief of right ventricular outflow tract obstruction late after repair of congenital heart defects. Circulation, 2006. 113(17): p. 2037-44.	1
22	Cubeddu, R.J. and Z.M. Hijazi, Bailout perventricular pulmonary valve implantation following failed percutaneous attempt using the Edwards Sapien transcatheter heart valve. Catheter Cardiovasc Interv, 2011. 77(2): p. 276-80.	3
23	Demkow, M., et al., Percutaneous pulmonary valve implantation preceded by routine prestenting with a bare metal stent. Catheter Cardiovasc Interv, 2011. 77(3): p. 381-9.	1
24	Demkow, M., et al., Percutaneous edwards SAPIEN() valve implantation for significant pulmonary regurgitation after previous surgical repair with a right ventricular outflow patch. Catheter Cardiovasc Interv, 2014. 83(3): p. 474-81.	1
25	Dilber, D., et al., Percutaneous pulmonary valve implantation and surgical valve replacement in patients with right ventricular outflow tract dysfunction--a complementary treatment concept. Int J Cardiol, 2013. 169(1): p. e3-5.	6
26	Dworakowski, R., et al., Treatment of acquired valvular heart disease: percutaneous alternatives. Clin Med, 2010. 10(2): p. 181-7.	1

27	Eicken, A., et al., Percutaneous pulmonary valve implantation: two-centre experience with more than 100 patients. Eur Heart J, 2011. 32(10): p. 1260-5.	
28	Ersboll, M. and L. Sondergaard, [Percutaneous stented pulmonary valve implantation]. Ugeskr Laeger, 2010. 172(13): p. 1030-4.	7
29	Ewert, P., E. Horlick, and F. Berger, First implantation of the CE-marked transcatheter Sapien pulmonic valve in Europe. Clin Res Cardiol, 2011. 100(1): p. 85-7.	3
30	Faza, N., et al., Single-center comparative outcomes of the Edwards SAPIEN and Medtronic Melody transcatheter heart valves in the pulmonary position. Catheter Cardiovasc Interv, 2013. 82(4): p. E535-41.	1
31	Frigiola, A., J. Nordmeyer, and P. Bonhoeffer, Percutaneous pulmonary valve replacement. Coron Artery Dis, 2009. 20(3): p. 189-91.	6
32	Frigiola, A., et al., Current approaches to pulmonary regurgitation. Eur J Cardiothorac Surg, 2008. 34(3): p. 576-80; discussion 581-2.	1
33	Gillespie, M.J., et al., Melody valve implant within failed bioprosthetic valves in the pulmonary position: a multicenter experience. Circ Cardiovasc Interv, 2012. 5(6): p. 862-70.	
34	Girona, J., P. Betrian, and G. Marti, Percutaneous implantation of a pulmonary valve. Rev Esp Cardiol, 2009. 62(9): p. 1072-4.	6
35	Godart, F., et al., [An experimental model of pulmonary valve implantation: a percutaneous and transventricular approach without cardiopulmonary bypass]. Arch Mal Coeur Vaiss, 2007. 100(5): p. 394-7.	7
36	Guccione, P., et al., Transcatheter pulmonary valve implantation in native pulmonary outflow tract using the Edwards SAPIEN transcatheter heart valve. Eur J Cardiothorac Surg, 2012. 41(5): p.	3

	1192-4.	
37	Haas, N.A., et al., Percutaneous implantation of the Edwards SAPIEN() pulmonic valve: initial results in the first 22 patients. Clin Res Cardiol, 2013. 102(2): p. 119-28.	
38	Hasan, B.S., et al., Short-term performance of the transcatheter Melody valve in high-pressure hemodynamic environments in the pulmonary and systemic circulations. Circ Cardiovasc Interv, 2011. 4(6): p. 615-20.	1
39	Huber, C.H., et al., Valved stents for transapical pulmonary valve replacement. J Thorac Cardiovasc Surg, 2009. 137(4): p. 914-8.	4
40	Jimenez, V.A., et al., Extrinsic compression of the left anterior descending coronary artery during percutaneous pulmonary valve implantation. JACC Cardiovasc Interv, 2014. 7(2): p. 224-5.	3
41	Kenny, D. and Z.M. Hijazi, State-of-the-art percutaneous pulmonary valve therapy. Expert Rev Cardiovasc Ther, 2012. 10(5): p. 589-97.	6
42	Kenny, D., et al. 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, 2011. 58, 2248-56 DOI: 10.1016/j.jacc.2011.07.040.	
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44	Khambadkone, S., Percutaneous pulmonary valve implantation. Ann Pediatr Cardiol, 2012. 5(1): p. 53-60.	1
45	Khambadkone, S. and P. Bonhoeffer, Percutaneous implantation of pulmonary valves. Expert Rev Cardiovasc Ther, 2003. 1(4): p. 541-8.	9
46	Khambadkone, S. and P. Bonhoeffer, Nonsurgical pulmonary valve	1

	replacement: why, when, and how? Catheter Cardiovasc Interv, 2004. 62(3): p. 401-8.	
47	Khambadkone, S. and P. Bonhoeffer, Percutaneous pulmonary valve implantation. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu, 2006: p. 23-8.	9
48	Khambadkone, S., et al., Percutaneous pulmonary valve implantation in humans: results in 59 consecutive patients. Circulation, 2005. 112(8): p. 1189-97.	10
49	Khambadkone, S., J. Nordmeyer, and P. Bonhoeffer, Percutaneous implantation of the pulmonary and aortic valves: indications and limitations. J Cardiovasc Med (Hagerstown), 2007. 8(1): p. 57-61.	1
50	Lee, Y.S. and H.D. Lee, Percutaneous pulmonary valve implantation. Korean Circ J, 2012. 42(10): p. 652-6.	6
51	Lurz, P. and P. Bonhoeffer, Percutaneous implantation of pulmonary valves for treatment of right ventricular outflow tract dysfunction. Cardiol Young, 2008. 18(3): p. 260-7.	6
52	Lurz, P., P. Bonhoeffer, and A.M. Taylor, Percutaneous pulmonary valve implantation: an update. Expert Rev Cardiovasc Ther, 2009. 7(7): p. 823-33.	6
53	Lurz, P., et al., Percutaneous pulmonary valve implantation: impact of evolving technology and learning curve on clinical outcome. Circulation, 2008. 117(15): p. 1964-72.	
54	Lurz, P., et al., Percutaneous pulmonary valve implantation. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu, 2009: p. 112-7.	9
55	Lurz, P., et al., Impact of reduction in right ventricular pressure and/or volume overload by percutaneous pulmonary valve implantation on biventricular response to exercise: an exercise stress real-time CMR study. Eur Heart J, 2012. 33(19): p. 2434-41.	9
56	Lurz, P., et al., Early versus late functional outcome after successful	9

	percutaneous pulmonary valve implantation: are the acute effects of altered right ventricular loading all we can expect? J Am Coll Cardiol, 2011. 57(6): p. 724-31.	
57	Lurz, P., 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. 119(23): p. 2995-3001.	1
58	Lurz, P., et al., Improvement in left ventricular filling properties after relief of right ventricle to pulmonary artery conduit obstruction: contribution of septal motion and interventricular mechanical delay. Eur Heart J, 2009. 30(18): p. 2266-74.	9
59	Luthra, S., et al., Transventricular pulmonary valve implantation in corrected truncus arteriosus. Ann Thorac Surg, 2012. 93(2): p. 660-1.	3
60	Lutter, G., et al., Percutaneous tissue-engineered pulmonary valved stent implantation. Ann Thorac Surg, 2010. 89(1): p. 259-63.	1
61	MacDonald, S.T., M. Carminati, and G. Butera, Percutaneous implantation of an Edwards SAPIEN valve in a failing pulmonary bioprosthesis in palliated tetralogy of Fallot. Eur Heart J, 2011. 32(12): p. 1534.	3
62	Mahgerefteh, J., N.J. Sutton, and R.H. Pass, Use of the Melody transcatheter pulmonary valve as a "covered stent" to repair conduit perforation during pulmonary valve implantation. Catheter Cardiovasc Interv, 2013. 81(6): p. 980-4.	3
63	Malekzadeh-Milani, S., M. Patel, and Y. Boudjemline, Folded Melody valve technique for complex right ventricular outflow tract. EuroIntervention, 2014. 9(10): p. 1237-40.	1
64	Martins, J.D., et al., Percutaneous pulmonary valve implantation: initial experience. Rev Port Cardiol, 2010. 29(12): p. 1839-46.	5

65	Maschietto, N. and O. Milanesi, A concert in the heart: bilateral Melody valve implantation in the branch pulmonary arteries. J Invasive Cardiol, 2013. 25(4): p. E69-71.	1
66	McElhinney, D.B., et al., Infective endocarditis after transcatheter pulmonary valve replacement using the Melody valve: combined results of 3 prospective North American and European studies. Circ Cardiovasc Interv, 2013. 6(3): p. 292-300.	1
67	McElhinney, D.B., et al., 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. Circ Cardiovasc Interv, 2011. 4(6): p. 602-14.	9
68	McElhinney, D.B., et al., Short- and medium-term outcomes after transcatheter pulmonary valve placement in the expanded multicenter US melody valve trial. Circulation, 2010. 122(5): p. 507-16.	
69	McElhinney, D.B. and J.T. Hennesen, The Melody(R) valve and Ensemble(R) delivery system for transcatheter pulmonary valve replacement. Ann N Y Acad Sci, 2013. 1291: p. 77-85.	3
70	Metzner, A., et al., Percutaneous pulmonary valve replacement: autologous tissue-engineered valved stents. Cardiovasc Res, 2010. 88(3): p. 453-61.	1
71	Milburn, K., V. Bapat, and M. Thomas, Valve-in-valve implantations: is this the new standard for degenerated bioprostheses? Review of the literature. Clin Res Cardiol, 2014.	6
72	Moiduddin, N., et al., Effect of transcatheter pulmonary valve implantation on short-term right ventricular function as determined by two-dimensional speckle tracking strain and strain rate imaging. Am J Cardiol, 2009. 104(6): p. 862-7.	9
73	Moiduddin, N., et al., Strain echocardiographic assessment of	3

	ventricular function after percutaneous pulmonary valve implantation. Congenit Heart Dis, 2012. 7(4): p. 361-71.	
74	Mollet, A., et al., Off-pump replacement of the pulmonary valve in large right ventricular outflow tracts: a transcatheter approach using an intravascular infundibulum reducer. Pediatr Res, 2007. 62(4): p. 428-33.	1
75	Momenah, T.S., et al., Extended application of percutaneous pulmonary valve implantation. J Am Coll Cardiol, 2009. 53(20): p. 1859-63.	1
76	Morray, B.H., et al., Risk of coronary artery compression among patients referred for transcatheter pulmonary valve implantation: a multicenter experience. Circ Cardiovasc Interv, 2013. 6(5): p. 535-42.	1
77	Muller, J., et al., Improved exercise performance and quality of life after percutaneous pulmonary valve implantation. Int J Cardiol, 2014.	1
78	Mullins, C.E., Off-label use of percutaneous pulmonary valved stents in the right ventricular outflow tract: time to rewrite the label? Catheter Cardiovasc Interv, 2013. 81(6): p. 996.	1
79	Nordmeyer, J., L. Coats, and P. Bonhoeffer, Current experience with percutaneous pulmonary valve implantation. Semin Thorac Cardiovasc Surg, 2006. 18(2): p. 122-5.	10
80	Nordmeyer, J., et al., Percutaneous pulmonary valve-in-valve implantation: a successful treatment concept for early device failure. Eur Heart J, 2008. 29(6): p. 810-5.	1
81	Nordmeyer, J., et al., Risk stratification, systematic classification, and anticipatory management strategies for stent fracture after percutaneous pulmonary valve implantation. Circulation, 2007. 115(11): p. 1392-7.	1

82	Nordmeyer, J., T.Y. Lee, and P. Bonhoeffer, Percutaneous pulmonary valve implantation: a 5-year projection. Am Heart Hosp J, 2006. 4(3): p. 205-6.	6
83	Nordmeyer, J., et al., Pre-stenting with a bare metal stent before percutaneous pulmonary valve implantation: acute and 1-year outcomes. Heart, 2011. 97(2): p. 118-23.	1
84	Nordmeyer, J., et al., Effective transcatheter valve implantation after pulmonary homograft failure: a new perspective on the Ross operation. J Thorac Cardiovasc Surg, 2009. 138(1): p. 84-8.	1
85	Odemis, E., et al., Percutaneous pulmonary valve implantation; first experiences from Turkey. Anadolu Kardiyol Derg, 2013. 13(4): p. 409-10.	1
86	Odemis, E., et al., Percutaneous pulmonary valve implantation using Edwards SAPIEN transcatheter heart valve in different types of conduits: initial results of a single center experience. Congenit Heart Dis, 2013. 8(5): p. 411-7.	3
87	Odenwald, T. and A.M. Taylor, Pulmonary valve interventions. Expert Rev Cardiovasc Ther, 2011. 9(11): p. 1445-57.	1
88	Oosterhof, T., M.G. Hazekamp, and B.J. Mulder, Opportunities in pulmonary valve replacement. Expert Rev Cardiovasc Ther, 2009. 7(9): p. 1117-22.	6
89	Pedra, C.A., et al., Percutaneous stent implantation to stenotic bioprosthetic valves in the pulmonary position. J Thorac Cardiovasc Surg, 2002. 124(1): p. 82-7.	1
90	Peer, S.M. and P. Sinha, Percutaneous pulmonary valve implantation after Ross-Konno aortoventriculoplasty: A cautionary word. J Thorac Cardiovasc Surg, 2014.	3
91	Plymen, C.M., et al., Electrical remodeling following percutaneous pulmonary valve implantation. Am J Cardiol, 2011. 107(2): p. 309-	1

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92	Quill, J.L., et al., Images in cardiovascular medicine. Direct visualization of a transcatheter pulmonary valve implantation within the visible heart: a glimpse into the future. Circulation, 2007. 116(22): p. e548.	1
93	Qureshi, A.M., R.A. Krasuski, and L.R. Prieto, Percutaneous pulmonary valve implantation in left pulmonary artery branch in a patient with a functional single lung. J Invasive Cardiol, 2012. 24(9): p. E202-4.	1
94	Raikou, M., et al., An assessment of the cost of percutaneous pulmonary valve implantation (PPVI) versus surgical pulmonary valve replacement (PVR) in patients with right ventricular outflow tract dysfunction. J Med Econ, 2011. 14(1): p. 47-52.	1
95	Ringewald, J.M. and E.J. Suh, Transcatheter pulmonary valve insertion: when, how, and why. Cardiol Young, 2012. 22(6): p. 696-701.	1
96	Romeih, S., et al., Delayed improvement of right ventricular diastolic function and regression of right ventricular mass after percutaneous pulmonary valve implantation in patients with congenital heart disease. Am Heart J, 2009. 158(1): p. 40-6.	9
97	Ruzyllo, W., et al., [POL-PAVTI--Polish report on transcatheter pulmonary artery valve implantation of Melody-Medtronic prosthesis in the first 14 patients in Poland]. Kardiol Pol, 2009. 67(10): p. 1155-61.	5
98	Schievano, S., et al., Percutaneous pulmonary valve implantation based on rapid prototyping of right ventricular outflow tract and pulmonary trunk from MR data. Radiology, 2007. 242(2): p. 490-7.	1
99	Schievano, S., et al., Finite element analysis of stent deployment: understanding stent fracture in percutaneous pulmonary valve	1

	implantation. J Interv Cardiol, 2007. 20(6): p. 546-54.	
100	Schmitt, C.A., Interventional cardiology: percutaneous pulmonary valve implantation: 1-year safety and efficacy reported in German study. Nat Rev Cardiol, 2011. 8(4): p. 186.	9
101	Secchi, F., et al., Cardiac magnetic resonance before and after percutaneous pulmonary valve implantation. Radiol Med, 2013.	
102	Thakkar, B., T. Madan, and A.J. Ashwal, Transcatheter right ventricular outflow tract stenting in children with postoperative infundibular stenosis and preserved pulmonary valve function. J Invasive Cardiol, 2013. 25(7): p. E151-4.	1
103	Thanopoulos, B.V., G. Giannakoulas, and C.A. Arampatzis, Percutaneous pulmonary valve implantation in the native right ventricular outflow tract. Catheter Cardiovasc Interv, 2012. 79(3): p. 427-9.	3
104	Vezmar, M., et al., Percutaneous pulmonary valve implantation in the young 2-year follow-up. JACC Cardiovasc Interv, 2010. 3(4): p. 439-48.	
105	von Wattenwyl, R., et al., Implantation of a catheter-based self-expanding pulmonary valve in congenital heart surgery: results of a pilot study. Eur J Cardiothorac Surg, 2011. 40(3): p. 552-6.	3
106	Wyller, V.B., et al., [Percutaneous catheter-based implantation of artificial pulmonary valves in patients with congenital heart defects]. Tidsskr Nor Laegeforen, 2011. 131(13-14): p. 1289-93.	5
107	Zahn, E.M., et al., 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. J Am Coll Cardiol, 2009. 54(18): p. 1722-9.	9
108	Zong, G.J., et al., [Transcatheter pulmonary valve replacement in sheep: 6-month evaluation of self-expanding valved stents].	4

	Zhonghua Xin Xue Guan Bing Za Zhi, 2008. 36(2): p. 151-5.	

Exclusion criteria*

1. Not Related
2. Protocol
3. Case report or descriptive article
4. Non clinical studies
5. Non English
6. Review article
7. Not full article
8. Duplicate
9. Data from same study
10. Other product

Appendix III Summary of Included Studies

Asoh 2010		
Method	Retrospective study (U.S)	
Participants	14 children undergoing PPVI into a bioprosthetic pulmonary valve	
	Inclusion criteria : all children who underwent PPVI from October 2005 to February 2008 Exclusion criteria : received a valve implantation in other than a bioprosthetic valve	
	Patient Characteristics	
	Gender	M:7 F:7
	Primary diagnosis	Tetralogy of Fallot (n=4) Pulmonary atresia with VSD (n=3) Truncus arteriosus (n=4) Double outlet right ventricle (n=2)
	RVOT morphology	Hancock conduit (n=11) Native outflow tract with valve implantation (n=3)
	Type of prosethetic valve	Symbion (n=2) Hancock (n=12)
	Time from prosthetic valve implantation to PPVI	10.4±4.0 years
	Age (Range)	15.4±2.0 (13.0-19.0) years
	Body Weight (Range)	56.8±7.5 (44.2-71.7) kg
	Indication	Predominant stenosis (n=2) Predominant regurgitation (n=2) Combined lesion (n=10)

<table>
<tr><td></td><td>Clinical symptoms</td><td colspan="3">Exercise intolerance (n=5)
Dyspnea (n=2)
Chest pain (n=1)
Arrhythmia (n=1)
Asymptomatic (n=5)</td></tr>
<tr><td>Intervention</td><td colspan="4">Melody™ transcatheter pulmonary valve stent mounted on Ensemble™ delivery system</td></tr>
<tr><td rowspan="11">Outcome & Result</td><td colspan="4">Immediate Hemodynamic results</td></tr>
<tr><td></td><td>Before</td><td>After</td><td>P value</td></tr>
<tr><td>Right Ventricular pressure (mmHg)</td><td>62.2 ± 21.1 (34.0-11.0)</td><td>42.4 ± 11.4 (29.0-60.0)</td><td>P<0.05</td></tr>
<tr><td>RVOT pressure gradients (mmHg)</td><td>36.7 ± 19.4 (7.0-81.0)</td><td>12.9 ± 7.3 (2.0-32.0)</td><td>P<0.05</td></tr>
<tr><td>Ratio of RVP to aortic pressure (AoP) (%)</td><td>72 ± 19 (47-113)</td><td>45 ± 10 (32-61)</td><td>P<0,001</td></tr>
<tr><td>RV end-distolic pressure (mmHg)</td><td>9.8 ± 4.8 (4.0-22.0)</td><td>9.3 ± 2.9 (4.0-14.0)</td><td>P=0.6</td></tr>
<tr><td>Angiography in the main PA</td><td></td><td>Significant improvement</td><td></td></tr>
<tr><td colspan="4">Procedural Complications & Hospital stay
One child (7.1%) had femoral artery pseudoaneurysm − hospital stay: 3 days
Others discharged within 2 days</td></tr>
<tr><td colspan="4">Immediate echocardiographic findings (within 24 hrs)</td></tr>
<tr><td></td><td>Before</td><td>After</td><td>p value</td></tr>
<tr><td>RVP (mmHg)</td><td>82.2 ± 15.6 (50.0-110.0)</td><td>61,0 ± 10.0 (48.0-80.0)</td><td>P<0.01</td></tr>
</table>

	RVOT gradient (mmHg)	59.6±26.8 (19.0-106.0)	41.0±19.1 (21.0-96.0)	P<0.05
	Grade of PR	3.6±0.8	0.6±0.9	P<0.001
	Time related changes in Echocardiographic data At latest follow-up (mean 12.9±9.8 months) Mean RVP : 52.1±14.4mmHg RVOT: 28.9±12.7 mmHg RVP/AoP ratio : 48±15% Increase in aortic valve annulus diameters (p<0.001) Increase in LV end-diastolic dimensions (p=0.01) No change in the degree of PR compared to immediately after PPVI			
	Freedom from re-intervention 3 months: 100±0 % 12 months: 91.7±7.8 % 25 months: 81.5±12.0 % 32 months: 81.5±12.0 %			
Notes				

Cochrane's Risk of Bias		
Item	Authors' judgment	Description
Adequate sequence generation?	No	Non-randomized
Allocation concealment	No	Non randomized/Retrospective study
Blinding	No	Non randomized/Retrospective study

Butera 2012		
Method	Prospective, observational, multicenter registry (Italia)	
Participants	October 2007 to October 2010, 63 patients were included in the registry	
	Inclusion criteria: age >5 years, weight >30kg, original conduit diameter ≥16mm and/or RVOT and pulmonary artery diameter <22mm, patients in NYHA class II-III-IV with a Doppler mean gradient >35mmHg and/or moderate pulmonary valve regurgitation, patients in >40mmHg and/or severe pulmonary valve regurgitation Exclusion criteria: active endocarditis, infection or sepsis, pregnancy, intravenous drug abuse, central veins occlusion, or significant obstruction	
	Patient Characteristics	
	N	63
	Age (yrs)	24 (11-65)
	Weight (kg)	60 (30-140)
	Sex (F/M)	31/32
	NYHA class	I: 15, II: 25, III: 16, IV: 7
	Original Diagnosis	Tetralogy of Fallot: 27, Trucus arteriosus: 5, Aortic valve disease (Ross Procedure): 9, Transposition of the great arteries: 7, Other: 15
	RVOT conduit type	Homograft : 33, Biological valved conduits: 28, Other: 5
	Primary indications for implantation	Stenosis: 21 (33%), Regurgitation: 12 (19%), Mixed: 30 (48%)
	Previous surgeries median (range)	2 (1-5)

<table>
<tr><td></td><td>Previous interventional cardiac catherization</td><td colspan="4">1 (0-4)</td></tr>
<tr><td>Intervention</td><td colspan="5">Melody valve and Ensemble delivery system</td></tr>
<tr><td rowspan="15">Outcome & Result</td><td colspan="5">Femoral approach was used in 59/63 patients, jugular approach was used in 4/63 patients</td></tr>
<tr><td colspan="5">Valve was delivered in 61 patients (97%). One aborted because of left coronary artery compression during balloon testing, other one aborted because of low gradient and mild pulmonary regurgitation.</td></tr>
<tr><td colspan="5">Early Result (Hemodynamic result)</td></tr>
<tr><td colspan="2"></td><td>Pre-procedure</td><td>Post-procedure</td><td>p</td></tr>
<tr><td colspan="2">RV systolic pressure, mmHg Median (range)</td><td>80 (70-100)</td><td>20 (10-30)</td><td><0.001</td></tr>
<tr><td colspan="2">Peak-to-peak systolic RV-PA gradient, mmHg Median (range)</td><td>45 (35-75)</td><td>10 (0-30)</td><td><0.001</td></tr>
<tr><td colspan="2">RV/Ao pressure ratio Median (range)</td><td>0.8 (0.6-1)</td><td>0.4 (0.15-0.7)</td><td><0.001</td></tr>
<tr><td colspan="5">Change of pulmonary regurgitation grade</td></tr>
<tr><td>Grade</td><td>Pre-procedure</td><td>Post-procedure</td><td colspan="2">Latest follow-up</td></tr>
<tr><td>0</td><td>0</td><td>30</td><td colspan="2">29</td></tr>
<tr><td>1</td><td>0</td><td>10</td><td colspan="2">9</td></tr>
<tr><td>2</td><td>5</td><td>1</td><td colspan="2">1</td></tr>
<tr><td>3</td><td>21</td><td>1</td><td colspan="2">1</td></tr>
<tr><td>4</td><td>16</td><td>0</td><td colspan="2">0</td></tr>
<tr><td colspan="5">Procedural Complications</td></tr>
<tr><td colspan="5">Complications occurred in nine patients (14%)</td></tr>
</table>

	Major complication occurred in two patients (pulmonary valve embolized, ventricular fibrillation) Other complications in seven patients (ventricular fibrillation)			
	Post procedural course			
	Hospital stay: 8 patients needed ICU stay for medium time of one day (range 1-45 days). Median hospital stay was five days (range 3-45 days) Mortality: One patient experienced early death			
	Follow-up data			
	Median 30 months (range 12-48 months) One external electrical cardioversion due to atrial fibrillation, three deaths, two bacterial endocarditis needing surgical explantation, and two significant stent fractures needing second valve implantation Freedom from valve failure and right ventricular outflow tract reintervention at latest follow-up was 81.4±9%.			
	Magnetic Imaging Resonance Data			
		Pre-procedure	Post-procedure (6 month)	P
	End-diastolic RV volume	90±36 (45-214)	69±23 (30-118)	0.01
	End-systolic RV volume	50±33 (21-200)	33±16 (13-77)	0.01
	RV ejection fraction	47±12 (14-67)	52±12 (34-76)	0.03
	End-diastolic LV volume	71±12 (31-131)	80±26 (31-143)	NS
	End systolic LV volume	30±11 (11-	34±16 (13-	NS

		69)	83)	
	LV ejection fraction	57±8 (44-71)	58±8 (41-70)	NS
	Regurgitant fraction (%)	35±10 (5-50)	8±7 (0-15)	0.001
Notes				
Cochrane's Risk of Bias				
Item	Authors' judgment		Description	
Adequate sequence generation?	No		Non-randomized	
Allocation concealment	No		Non randomized/Registry	
Blinding	No		Non randomized/Registry	

Eicken 2011	
	Multi-site, consecutive enrollment
Participants	December 2006 to July 2010, 102 consecutive patients who were scheduled for PPVII at the German Heart Centres Munich and Berlin
	Age >5 years, weight >20kg Conduit right ventricular outflow tract > (16) 18mm ≤22mm Severe pulmonary regurgitation, progredient RV dilation and reduced RV function Symptomatic patients with declining exercise tolerance Increased RV pressure A combination of stenosis and regurgitation with RV dysfunction and dilation

	Supraventricular or ventricular rhythm disturbances	
	Patient Characteristics	
	Gender	Female, 40; male, 62
	Diagnosis	TOF/PA, 61; TAC, 14; TGA, 9; AoS, 8; other, 10
	Conduit RV-PA	Homograft, 79; Contegra, 6; non-valved, 6; Hancock, 3 Shelhigh, 1; matrix, 1; Carpentier-Edwards, 1; none, 5
	Pre-stenting	Yes, 97; no, 5
	Age at PPVI (years)	21.5 (16.2-30.1)
	Weight (kg)	63.0 (54.2-75.9)
Intervention	Melody, Medtronic, Inc., Minneapolis, MN, USA	
Outcome	Immediate results of Percutaneous Pulmonary valve Implantation The systolic gradient between the right ventricle and the pulmonary artery was reduced from a median value of 37 mmHg (29-46mmHg) to 14 mmHg (9-17mmHg, $p<0.00001$) The ratio between systolic right ventricular and aortic pressure was decreased from a median value of 62% (53-76%) to 36% (30-42%, $p<0.001$) In patients with nearly normal RV pressure, pulmonary regurgitation was the prevailing cardiac lesion. Pulmonary regurgitation assessed by MRI was reduced from a median value of 16% (5-26%) to 1%(0-2%, $p<0.001$) The right ventricular end-diastolic volume index assessed by MRI decreased from a median value of 106 mL/m2 (93-133 mL/m) to median value of 90mL/m2 (71-108 mL/m2, $p<0.001$) before hospital discharge	

	The patients were discharged home at median 2 days after the intervention.	
Notes		
Cochrane's Risk of Bias		
Item	Authors' judgment	Description
Adequate sequence generation?	No	Described as nonrandomized
Allocation concealment	Unclear	Information not available
Blinding	No	Non randomized

Gillespie 2012		
Method	Multi-center, retrospective study	
Participants	Patients who underwent TPVI of a Melody to BPV in the pulmonary position at 8 centers in the United States between April 2007 and January 2010	
	Demographic and Diagnostic Data	
	Age, y	26 (3-63)
	Weight, kg	68 (16-199)
	Underlying anatomy	Tetralogy of Fallot 74%, Truncus arteriosus 7%, Pulmonary stenosis 7%, Dextrotransposition of the great arteries 4%, Aortic stenosis 4%, Double-outlet right ventricle 1%
	Biopresthetic valve type	Carpetier-Edwards Perimount 37%, Medtronic Hancock Conduit 37%,

		Medtronic Mosaic 7%, Medtronic Hancock 2 7%, Medtronic Freestyle 4%, Sorin Mitroflow 3%, Carpentier-Edwards aortic porcine 3%, St Jude Biocor 2%, Ionescu-Shiley 1%, St Jude Epic 1%
	Bioprosthetic valve size, mm	23 (16-29)
	Bioprosthetic valve age, y	9.1 (0.6-33)
Intervention	Melody valve implant within a surgically placed BPV	
Outcome	The peak RV-PA gradient decreased from 38.7±16.3 to 10.9±6.7 mmHg($p<0.001$) RV systolic and diastolic pressure fell from 71.6±21.7 to 46.7±15.9 mmHg and from 11±4.6 to 10.4±3.7mmHg, respectively (both $p<0.001$) The mean right artrial pressure decreased from 11.4±4.4 to 10.4±3.7 mmHg ($p=0.006$) The systolic and diastolic PA pressures increased from 32.7±14.1 to 36.2±15.7 mmHg ($p=0.02$) and from 12.8±5.1 to 17.2±7.1 mmHg ($p<0.001$) Freedom from reintervention on the Medlody vavle, which was identical to freedom from explant, was 97.2±2% at 1 year and 92±5% at 2 years Freedom from a diagnosis of Melody valve stent fracture was 98±2% at 1 year and 95±3% at 2 years	
	Pulmonary regurgitation: None 79%, Trivial or Mild 21%, Moderate or Severe 0%	

Notes		
Cochrane's Risk of Bias		
Item	Authors' judgment	Description
Adequate sequence generation?	No	Described as nonrandomized
Allocation concealment	Unclear	Information not available
Blinding	No	Non randomized

Haas 2013		
Method	Prospective (not specified any further)	
Participants	22 patients who has underlying primary diagnosis	
	Patient characteristics	
	Gender	Female 9, Male 13
	Age	21.7 (range 6-83)
	Weight	56.5kg (range 20-91)
	Primary diagnosis	Tetralogy of fallot 11 Pulmonary atresia 2 Truncusarteriosus 3 TGA/PS-Rastelli 1 Ross 2 Double outlet right ventricle 2 Absent pulmonary valve 1
	RVOT anatomy prior to valve implantation	Transanular patch 4 Bisoprosthesis 2 Homograft 5

		Contegra 11		
	Main hemodynamic diagnosis	Pulmonary stenosis 2 Pulmonary regurgitation 11 Combined PS/PI 9		
Intervention	PPVI using the Edwards SAPIEN™			
Outcome	Invasive hemodynamic data			
		Pre	Post	p
	RV-pressure systolic	61.2(±23.1)	41.2(±8.6)	<0.05
	PA-pressure systolic	25.8(±8.6)	33.9(±9.2)	<0.05
	PA-pressure diastolic	6.0 (±5.6)	14.6 (±4.3)	<0.05
	Systolic gradient	37.3 (±23.2)	6.9 (±5.3)	<0.05
	Pulmonary regurgitation			
	None/trivial	2	21	
	Mild	1	0	
	Moderate	9	0	
	Severe	10	0	
	Echocardiographic data			
	RV-pressure systolic	69.7(±25.6)	40.9(±10.3)	<0.05
	Flow velocity RVOT	3.7(±1.0)	2.3(±0.5)	<0.05

Cochrane's Risk of Bias		
Item	Authors' judgment	Description
Adequate sequence generation?	No	Described as nonrandomized
Allocation concealment	Unclear	Information not available

Blinding	No	Non randomized

Kenny 2011				
Method	Early phase I trial, international, multicenter, 1-arm, clinical trial			
Participants	Apr 2008 to May 2010, 36 patients from 4 centers were enrolled.			
	Demographics			
	Age	30. 3±15.1		
	Weight	73.4±22.9		
	Gender	Male 24, Female 12		
	Diagnosis	Tetralogy of Fallot 16 Ross procedure 11 Transposition of the great arteries 1 Other 8		
	NYHA	I 5, II 17, III 12, IV 2		
	Open heart surgeries	19.4 (1-5)		
	RVOT conduit types	Homograft 29, Other 7		
	Primary indication	Stenosis 15, regurgitation 19, mixed 2		
	RVOT pre-stenting	Stent placed at time of procedure 24 Stent placed before day of procedure 12		
Intervention	Edwards SAPIEN in the pulmonary position			
Outcome	Comparative TTE, MRI, CPET data			
		Pre	Post (6 months)	P
	Transthoracic echo			
	Conduit peak gradient	41.9±26.2	19.1±13.3	<0.001

	Conduit mean gradient	24.0±15.0	12.0±8.8	<0.001
	Estimated RV pressure	67.3±20.6	49.3±11.1	0.005
	Magnetic resonance imaging			
	Pulmonary regurgitant fraction	28.64±18.0	3.47±5.40	<0.001
	RV end-diastolic volume	130.9±62.6	86.9±19.6	0.02
	Cardiopulmonary exercise testing			
	Peak Vo2	22.1±9.4	23.1±8.0	0.09
	RQ at peak exercise	0.9±0.1	0.9±0.2	0.23

Cochrane's Risk of Bias		
Item	Authors' judgment	Description
Adequate sequence generation?	No	Described as nonrandomized
Allocation concealment	Unclear	Information not available
Blinding	No	Non randomized

Lurz 2008	
Method	Prospective study (no other information provided)
Participants	Sep 2000 to Feb 2007, 155 patients enrolled
	Inclusion criteria RV systolic pressure >2/3 of systemic plus symptoms, or

	RV systolic pressures >3/4 of systemic in absence of symptoms, and/or Moderate/severe PR and 1 of following criteria: Symptoms , sever RV dysfunction, severe RV dilation, impaired exercise capacity RVOT dimensions < 22 X 22 mm RVOT dimensions > 14 X 14 mm			
	Characteristics			
	Age	21.2 (7-17)		
	Diagnosis	Tetralogy of fallot 60.6% Double-outlet RV 5.8% TGA, VSD, PS 9% Ross procedure 7.7% Truncus arteriosus 11%		
	RVOT characteristics	Homograft 81.3% Hancock 7.1% Other conduit type 4.5% Patch-extended RVOT 1.3% Native outflow tract 3.2% Other 2.6%		
	NYHA	I 11%, II 52.9%, III 29%, IV 7.1%		
Intervention	Melody™			
Outcome	Pressure at Catheterization			
	Parameter	Pre	Post	P
	RV systolic pressure	63±18	45±13	<0.001
	RV end-diastolic pressure	12±4	10±5	<0.001
	PA systolic pressure	27±11	29±12	0.056
	PA diastolic pressure	10±4	14±9	<0.001

	RV-PA gradient	37±20	17±10	<0.001
	Aortic systolic pressure	94±15	101±16	<0.001
	Aortic diastolic pressure	54±10	58±10	<0.001
	RV-to-systemic pressure	69±19	45±14	<0.001

Cochrane's Risk of Bias		
Item	Authors' judgment	Description
Adequate sequence generation?	No	Described as nonrandomized
Allocation concealment	Unclear	Information not available
Blinding	No	Non randomized

McElhinney 2010		
Method	Prospective, nonrandomized, multi-center study	
Participants	From Jan 2007 through Aug 2009, 136 patients were enrolled	
	Characteristics	
	Gender	64% Male, 36% Female
	Median age	19 years (7-53 years)
	Original diagnosis	Tetralogy of fallot 48% Aortic valve disease after Ross operation 21% Transposition of the great arteries 11% Truncus arteriosus 10% Double-outlet right ventricle 6% Valvar pulmonary stenosis 2% Other 1%

	NYHA class	I 16%, II 67%, III 16%, IV 1%					
	Type of conduit	Homograft 76%, Bioporosthetic 19%, Synthetic 5%					
	Previously placed conduit stent	No 74%, single stent 17%, multiple stent 9%, no report 1%					
	Number of prior surgical conduit	1 (1-5)					
	Median (range) conduit/valve diameter at the time of surgical implantation	21 (16-28)					
Intervention	Melody™						
Outcome	Hemodynamic measures						
		Primary indication PR (n=65)			Primary indication Obstruction or Mixed (n=59)		
	Variable	Pre	Post	P	Pre	Post	p
	RV systolic pressure	61.6±20.6	47.2±15.0	0.001	69.4±12.9	44.7±10.9	0.001
	PA systolic pressure	34.8±14.6	34.9±13.1	0.94	30.1±16.8	31.5±11.1	0.9
	Peak RV-to PA gradient	28.1±15.7	12.7±7.4	0.001	43.7±11.4	14.4±5.7	0.001
	Aortic systolic pressure	93.8±13.5	112.5±20.9	0.001	89.7±12.7	104.8±17.2	0.001
	RV/aortic pressure ratio	0.65±0.19	0.42±0.12	0.001	0.78±0.15	0.43±0.12	0.001
	Echocardiography, MRI, ECG						
	Variable		Pre		Post (6 m)	P	

	Echocardiography (n=98)			
	RV pressure	73.5±17.9	55.0±14.6	0.001
	Mean RVOT gradient	33.4±15.0	20.0±8.6	0.001
	Maximum instantaneous RVOT gradient	55.0±23.1	32.9±13.8	0.001
	MRI (n=80)			
	RV end-diastolic volume	205.8±90.2	172.7±76.3	0.001
	Indexed RV end-diastolic volume	125.1±49.2	103.0±39.5	0.001
	RV ejection fraction	43.2±14.1	42.6±12.3	0.9
	RV mass	67.3±27.3	57.5±19.3	0.001
	PR fraction	24.8±14.9	2.8±3.1	0.001

Cochrane's Risk of Bias		
Item	Authors' judgment	Description
Adequate sequence generation?	No	Described as nonrandomized
Allocation concealment	Unclear	Information not available
Blinding	No	Non randomized

Secchi 2013		
Method	Retrospective study (other information not available)	
Participants	Jan 2008 to Jun 2010 in 27 consecutive patients	
	Demographics	
	Gender	12 females, 15 males

	Age	22±9 years		
	Original diagnosis	Tetralogy of Fallot 26%, Aortic valve disease 26%, transposition of great arteries 16%, double outlet right ventricle 11%, truncus arteriosus 7%, pulmonary atresia 7%, pulmonary stenosis 7%		
	RVOT conduit type	Homograft 41%, shelhigh 15%, matrix 11%, monoscupid homograft 7%, hancock 7%, contegra 4%, ionescu-shiley 4%, conduit not implanted 11%		
Intervention	Melody pulmonary valve implantation			
Outcome	Cardiac magnetic resonance data			
		Pre	Post	p
	RV EDVI	79±42	64±21	0.050
	RV ESVI	34±41	30±14	0.021
	RV EF	49±13	54±12	0.018
	LV EDVI	64±15	73±21	0.034
	LV ESVI	30±9	33±4	0.508
	LV EF	54±7	57±10	0.147
	RF	14±18	2±5	0.013
	PG	36±15	13±15	<0.001

Cochrane's Risk of Bias		
Item	Authors' judgment	Description
Adequate sequence generation?	No	Described as nonrandomized

Allocation concealment	Unclear	Information not available
Blinding	No	Non randomized

Vezmar 2010		
Method	Prospective (other information not available)	
Participants	Between Oct 2005 and Dec 2008, 28 adolescents	
	Inclusion criteria RV systolic pressure >2/3 ysstemic with clinical symptoms or RV systolic pressure >3/4 of systemic with no clinical symptoms and/or Moderate to severe PI and 1 of the following − severe RV dysfunction, severe RV dialation, Decreased exercise capacity, arrhythmias RVOT dimentions <22X22 mm, RVOT dimentions >14 X14 mm, weight >20kg	
	Exclusion criteria Age<5 yrs or weight <20 kg, pregnancy, occluded central veins, active infection, coronary anatomy at risk of compression at the time of implant	
	Group Characteristics	
	Children	28
	Gender	Male 16, Female 12
	Primary Diagnosis	PA/VSD 32%, TOF 25%, PAT 18%, DORV, TAG/PS 7%, AI 7%, ccTGA/PS 7%, AoA/VSD 4%
	Primary repair	RV-PA conduit 61%, TAP 21%, Ross 4%, Ross-Konno 4%, Yasui 4%, REV 6%
	Age at	1.7±1.9

	primary repair			
Intervention	Melody™ valve implantation			
Outcome	Cauterization data			
		Before PPVI	After PPVI	p
	RV-PA gradient, mmHg	36±15	12±7	<0.001
	RVSp, mmHg	61±16	41±11	<0.001
	RVDp, mmHg	11±5	10±4	0.04
	MPAPs, mmHg	26±8	30±9	0.02
	MPAPd, mmHg	11±4	15±5	0.003
	AoPs, mmHg	86±10	94±11	0.001
	AoPd, mmHg	56±7	61±8	0.001
	RV/Ao	70±16	44±11	<0.001
	MRI Volumetric Data			
	RVEDV	149±49	144±35	0.005
	RVESV	85±48	63±29	0.005
	RV effSV	44±12	48±8	0.04
	RVEF	42±15	46±13	0.43
	RV CO	2.7±0.5	3.4±0.8	0.04
	LVEDV	90±19	97±20	0.007
	LVESV	37±10	39±11	0.6
	LVEF	50±13	57±14	0.02
	LV effSV	56±9	60±7	0.24
	LV CO	2.7±0.6	3.2±0.6	0.02

	RV/LVEDV	1.75±0.5	1.24±0.27	0.001
	PR	24±10	7±7	<0.001
Notes				
Cochrane's Risk of Bias				
Item	Authors' judgment		Description	
Adequate sequence generation?	No		Described as nonrandomized	
Allocation concealment	Unclear		Information not available	
Blinding	No		Non randomized	

Appendix IV Abbreviation

CHD	Congenital Heart Disease
DORV	Double Outlet Right Ventricle
MRI	Magnetic Resonance Imaging
PA	Pulmonary Artery
PPV	Percutaneous Pulmonary Valve
PPVI	Percutaneous Pulmonary Valve Implantation
RV	Right Ventricle
RVOT	Right Ventricle Outflow Tract
RVP	Right Ventricular Pressure
RV-PA	Right Ventricle to Pulmonary Artery
TA	Truncus Arteriosus
TGA	Transposition of Great Arteries
ToF	Tetralogy of Fallot

논 문 초 록

경피적 폐동맥판 치환술은 2000년에 첫 시도되어 십여 년 동안 사용되어 왔다. 본 연구는 경피적 폐동맥판 치환술 이후 이의 임상결과에 대하여 연구된 논문을 체계적 문헌고찰 및 메타분석 하는데 목표하였다.

문헌검색은 PubMed와 Cochrane 데이터베이스를 사용하였으며, NECA 가이드라인에 준하여 2014년 4월에 시행되었다. 599개의 문헌이 검색되었으며, 이중 2005년 이후 출간된 10개의 문헌이 본 연구에 사용되었다. 메타분석은 RevMan 소프트웨어를 사용하여 분석하였다.

분석된 즉시적 혈류역학, MRI, 혈류역류에 대한 임상결과는 유의한 유효성을 보여주었다. RV systolic pressure 는 유의하게 감소하였으며 (mean difference: 20.03mmHg, 95%: 17.95, 12.11), RV diastolic 도 유의하게 감소하였고(mean difference: 1.69mmHg, 95%: 0.94, 2.26), RV-PA gradient 도 유의한 감소를 보였으며(mean difference: 18.96, 95%: 15.94, 21.99), End-diastolic RV volume 또한 유의한 감소를 보였다 (mean difference: 26.92, 95%: 16.06, 37.77).

본 연구는 경피적 폐동맥판 치환술 이후의 안전성 및 유효성 개선의 유의한 차이를 보였다.

주요어 : 경피적 폐동맥판 치환술, 체계적 문헌고찰, 메타분석

학 번 : 2011-23867