# Percutaneous heart valve implantation in congenital and degenerative valve disease. A rapid Health Technology Assessment.

*KCE reports 95C*

Federaal Kenniscentrum voor de Gezondheidszorg
Centre fédéral d'expertise des soins de santé
Belgian Health Care Knowledge Centre
2008

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# Percutaneous heart valve implantation in congenital and degenerative valve disease. A rapid Health Technology Assessment.

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# Executive summary

# SCOPE

This Health Technology Assessment report summarises current evidence supporting the use of percutaneous heart valves in degenerative aortic valve and congenital pulmonary outflow tract disease, as compared to conservative medical therapy or traditional surgical valve replacement.

Percutaneous aortic valve insertion has been reported since 2002 for the treatment of calcific aortic valve stenosis in elderly patients considered to be at unacceptably high risk for conventional surgery. Percutaneous pulmonary valve insertion has been first reported in the year 2000. The procedure is restricted to patients with congenital heart disease in whom degeneration of a previously surgically reconstructed right ventricular outflow tract has occurred.

# PERCUTANEOUS AORTIC VALVE

## Clinical background

Aortic stenosis (AS) is the most common valvular heart disease in adults and generally is degenerative in origin, resulting from a progressive age-dependent build-up of calcium in the aortic valve. Its prevalence is strongly related to population ageing, and as such is expected to represent an increasingly important public health problem. Pharmacological treatment of patients with symptomatic AS results in a temporary alleviation of symptoms but curing AS requires surgical valve replacement. This is a time-honoured technique which has produced excellent results in an estimated one million patients over the last four decades. Experienced surgeons can perform it with single-digit mortality, even in octogenarians. Because of population ageing, AS is becoming more prevalent and often, these patients also present with significant co-morbidities that hitherto sometimes impeded surgeons to proceed to surgical correction of the valvular disease, not least because of the expected high perioperative mortality rates in frail and elderly high-risk subjects. This observation has led to the development of percutaneous aortic valve (PAV) technology, which by its less invasive nature, is believed to represent a safer treatment modality for these elderly patients.

It is not clear how many patients could benefit from a PAV insertion because eligibility criteria for the time being are unclear. Conventional surgical isolated aortic valve replacements (AVR) are yearly performed in 1100 patients in Belgium. Belgian experts estimate that PAV could currently be justified in approximately 250 patients per year. This estimate, however, is dependent on further improvements and diffusion of the technique, and even more so on the criteria that will be used to define eligibility of patients.

## The PAV technology

The use of PAV at this moment is restricted to (mostly elderly) patients that are deemed inoperable or are considered at very high risk for conventional surgery, due to a variety of co-morbid conditions, such as chronic obstructive pulmonary disease, severe left ventricular dysfunction or general frailty. The operability of patients is based on clinical judgement by the clinician, supplemented with information obtained from an operative risk score - very often the EuroSCORE - that provides an estimation of the operative mortality risk. However, the validity of this risk tool for estimating the surgical risk incurred by high-risk patients has been heavily criticised.

At least 20 types of PAVs are currently tested at various stages of development. For the time being, two types have received CE marking and are available for clinical use: the Edwards-Sapien and the CoreValve. The Edwards-Sapien PAV, is a bioprosthesis that is made of bovine pericardium and is integrated into a stainless steel, balloon expandable stent frame. The CoreValve PAV consists of a bioprosthetic porcine pericardial tissue valve that is mounted and sutured in a self-expanding nitinol stent.

After predilatation of the native stenotic aortic valve, in the *transfemoral approach*, the PAV is advanced from the femoral artery, over a guidewire, through the native valve. The Edwards-Sapien PAV is deployed within the aortic valve orifice by means of a balloon. The CoreValve on the other hand is self-expandable and is contained within a sheath from which it is pushed, once adequate positioning of the device within the native aortic valve is accomplished. The suitability for patients to be treated with a PAV is restricted by aortic annulus dimensions, and depends on the accessibility of a patient's arterial tree as well. The access can e.g. be rendered impossible due to severe iliofemoral atheromatous disease, a problem which has been overcome by an alternative procedure, the *transapical approach*. Here, PAV delivery directly occurs from the left ventricular apex, obviously involving a mini-thoracotomy. Patients treated by the transapical approach have an even higher operative risk than those in whom a transfemoral approach is not hindered by severe atheromatous vascular disease.

## Clinical effectiveness

There is no data on the performance of PAV based on randomised controlled trials (RCT). Only observational data from series, published in peer reviewed journals (300 cases), and data presented at cardiology meetings (>1600 cases) are available. Published case series indicate that PAV insertion is feasible in the hands of experienced operators in up to 90% of eligible patients. Unpublished data report success rates up to 100%. PAV insertion in these populations however seems to be a risky intervention with one-month mortality rates from 6.4 to 13.2% in transfemoral PAV insertion and 8.0 to 22.5% in transapical series from experienced centres. In these patients, it is uncertain what their mortality would have been if they had been operated conventionally or treated medically.

Vascular complications of PAV insertion especially occur with the transfemoral approach in 10-15% of patients. Stroke has also been observed more frequently in the transfemoral approach, and is reported in 3-10% of cases.

The short term efficacy of PAV seems to be good. Patients in whom a PAV has been successfully inserted are reported to experience an improvement in their New York Heart Association (NYHA) functional class, in accordance with an improved valvular function by echocardiography and doppler. It is not clear what the real impact of PAV would be on a generic measurement of Quality of Life (QoL), since these patients have additional (severe) co-morbidities that affect their QoL, even after successful PAV insertion.

Few 6-month survival data have been published, but case series presented at 2008 cardiology meetings, report high mortality rates, ranging from 10-21.7% in transfemoral series and 26.1-45.0% in transapical series.

There is practically no data on the long term (>1 year) clinical effectiveness of PAV insertion as compared to medical therapy or conventional surgery. Long term performance is related to the impact of a potential residual aortic regurgitation resulting from a suboptimal positioning of the PAV, and to the service life of the valve. The latter may be a less important issue, given the limited life expectancy of the patients involved.

## Conclusions on PAV insertion

Although data from an increasing number of patients are presented at scientific meetings, these do not add to our understanding of the potential of this new technology. The methodological shortcomings prevailing in the initial published series remain unaltered, i.e. the data presented are mere observational from selected and unrandomised patient groups. Therefore the conclusions of this KCE report are expected to remain valid until results from RCTs have become available.

It is not clear for which patients PAV is an appropriate alternative as compared to a conservative medical therapy or conventional surgery. Currently available data suggests that PAV insertion is feasible and provides at least short term (6 months-1 year) hemodynamic and clinical improvement. However, in patients that are considered for the procedure, life expectancy and QoL are not only determined by the aortic valve disease as such.

Age by itself and the natural history of the co-morbidities conditions (that remain unaffected by the anatomical correction of the AS), bear upon survival and on QoL. It is not clear whether PAV would improve these outcomes as compared to other treatment strategies.

Safety issues, demonstrated by a 30-days mortality rate of 6.4 to 22.5%, represent a major drawback for implementation of this technology. "High-surgical-risk" and "operability" status are poorly defined concepts and complicate the selection of patients and the interpretation of outcomes reported in case series. Recent observational data indicate that the EuroSCORE severely overestimates operative risk in high-risk patients undergoing an isolated surgical AVR. In surgical series from the Mayo Clinic, an estimated 30-day mortality of 23.6% sharply contrasted with an observed mortality of only 5.8%. Patients with a similar predicted operative risk (25.4%) enrolled in PAV series, had a 30-days mortality that was 6.4-13.2% in transfemoral, and 8.0-22.5% in transapical series. This suggests that patients with AS that are considered at high risk for conventional AVR, may actually present lower mortality rates if treated surgically than if treated by means of PAV insertion.

Six month mortality of patients treated by PAV is very high, and ranges from 10-21.7% in transfemoral series and 26.1-45.0% in transapical series questioning the appropriateness of this procedure. Presently, the intervention's cost-effectiveness cannot be reliably calculated because no objective input data are available.

These observations reinforce the contention that RCTs are badly needed to clarify the performance of PAV insertion. The ongoing US PARTNER-IDE RCT is expected to clarify (1) if patients that are inoperable are better off with PAV than with medical treatment, and (2) if patients at high risk for surgery have a lower risk with PAV than with conventional AVR.

# PERCUTANEOUS PULMONARY VALVE

## Clinical background

Some types of congenital malformations of the heart require surgical correction early in life, such as malformations in the right ventricular outflow tract (RVOT) in tetralogy of Fallot or truncus arteriosus. For some patients, this early repair only represents a temporary solution, and additional surgery later on, is needed. This consists in the construction of a valved conduit between the heart and the pulmonary artery. Because of outgrowth and/or degeneration of these valved conduits, patients have to undergo one or more repeat surgical interventions. In most cases, the repeat intervention is performed, not so much for symptomatic reasons, but rather to prevent the occurrence of heart failure and potentially lethal ventricular arrhythmias later in life. In order to try to limit the number of repeat operations, percutaneous pulmonary valve (PPV) insertion has been developed.

Based on the prevalence of congenital heart disease, experts estimate that in Belgium, yearly less than 50 such patients would benefit from PPV insertion. No substantial increase in the number of eligible patients is to be expected in the future, given the stability of the prevalence of congenital heart disease.

### The PPV technology

Published experience is essentially limited to one PPV type, the "Melody" valve manufactured by Medtronic. Investigators from 17 European centres have reportedly acquired experience with this device in 399 patients. Until May 2008, 556 Melody PPVs had been implanted worldwide, of which 10 were treated in a single Belgian centre.

The Melody PPV consists of a segment of a bovine jugular vein that contains a venous valve and is attached to a stent. The technique of PPV insertion is similar to that of the percutaneous dilatation and stenting of the native pulmonary valve as performed in congenital pulmonary stenosis. The procedure is performed under general anaesthesia and requires standard right heart catheterisation techniques, usually from a femoral vein.

A patient's suitability for PPV is dependent on the dimensions of the venous access route and a minimal body weight of 20 kg is needed. Furthermore, suitability depends on the dimensions of the RVOT that has to have a diameter of less than 22 mm and more than 14 mm.

### Clinical effectiveness

There is no data on the performance of PPV insertion based on RCTs. Published data essentially are restricted to case series originating from one single operator (Philipp Bonhoeffer, Paris and London). In his hands, PPV insertion is feasible in almost all patients selected for the procedure. The mortality risk of PPV insertion as reported in his most recently published series is very low (2/155). The incidence of procedural complications fell from 6% in the first cohort of 50 cases to 2.9% in the second cohort of 105 patients.

The short term (median follow-up 28 months) efficacy of PPV is good. Patients in whom a PPV has been successfully inserted have an adequate valvular function by echocardiography and doppler. In a cohort of 105 patients, a redo-valve implantation was needed in 13% of cases, within a follow-up period of 0-40 months.

The optimal timing of the procedure in order to prevent right ventricular failure and fatal ventricular arrhythmias is unknown. The long-term effectiveness as compared to a traditional strategy (watchful waiting until surgery is deemed necessary) is unknown. There are no data on the longevity of the implanted device.

### Conclusions on PPV insertion

In contrast to aortic stenosis (in high-risk elderly people), a conservative (i.e. medical) treatment is no option in symptomatic patients with a degenerated pulmonary valved conduit.

The feasibility and safety of PPV insertion is excellent, at least in the hands of one operator. Short term hemodynamic and clinical performance is good.

The timing of the procedure in asymptomatic patients, the service life of the device and its ability to postpone or prevent the occurrence of heart failure and fatal arrhythmias later in life remain unknown.

Data from RCTs is not available. It is regrettable that – to our knowledge – no RCT has been planned to assess the efficacy of this promising technology.

## PATIENT ISSUES

Before submitting patients to a percutaneous valve insertion, they should be well informed about the prevailing uncertainties surrounding the benefit they can expect from the procedure as compared to a conservative treatment or surgical valve replacement. Moreover, patients that are proposed a PPV insertion should be informed about the uncertainties concerning the optimal timing of the procedure and the potential for redo-interventions because of early device failure.

# COST CONSIDERATIONS

Currently, it is hard to perform a reliable economic evaluation of percutaneous valve technology, because there are no clinical studies with comparable populations in the intervention and control group(s). On the one hand, the cost of the initial intervention is higher due to the high cost of the device. In Belgium, the price for a biological valve prosthesis intended for standard surgical implantation is approximately €3 000 (incl. TAV). The price for the Edwards-Sapien PAV and the Medtronic Melody PPV was determined at €20 398.24 (incl. TAV). For the Corevalve Revalving PAV this was €19 610 (incl. TAV). It is not clear how this price was set. More transparency on this price setting is wishful.

On the other hand, a shorter hospital length of stay may positively impact on both costs and QoL. However, data on safety, efficacy/effectiveness, QoL (measured with a generic instrument) and costs should be gathered in the first place to be able to perform a reliable full economic evaluation.

# ORGANISATIONAL ISSUES

It is premature to discuss the organisational prerequisites for a nationwide percutaneous heart valves interventions program, as long as no hard effectiveness data have become available.

International experts point to a learning curve in the procedural success and stress the importance of a close collaboration between interventional cardiologists/paediatricians, surgeons and anaesthesiologists.

An uncontrolled diffusion of the technique has to be avoided.

# RECOMMENDATIONS

## THE PERCUTANEOUS AORTIC VALVE

A reimbursement of the PAV can currently not be defended because of patient safety concerns, and a poorly defined target population. Published data is not convincing that the procedural mortality risk related to PAV insertion is lower than the risk incurred by conventional surgery in comparable patients. Moreover, it is unclear which patients might benefit from the technology, because clinical effectiveness not only depends on the natural history of the aortic stenosis but also on the patient's life expectancy related to co-morbidities. The very high 6-month mortality rates render the appropriateness of the procedure questionable.

The conclusions of this report can be considered up-to-date as long as no data from an ongoing RCT have become available.

For ethical reasons, patients should only be subjected to PAV insertion within the boundaries of an RCT.

The decision whether to reimburse PAV technology is to be reconsidered when the results of the ongoing United States based RCT (PARTNER IDE) become available. If this RCT provides evidence on safety and effectiveness of the PAV, its acceptability (cost-effectiveness) and affordability (budget impact) need to be assessed.

The medical community should be well informed that the assignment of a European CE marking does not indicate that a device is safe for clinical use. It is desirable that, at least on a national, preferably on a European level, that a continuous monitoring is performed for (new) implants for which clinical safety is not proven. This would enable government to intervene and insure the patient's safety.

# THE PERCUTANEOUS PULMONARY VALVE

Although only a limited number of patients are eligible for PPV insertion (implying a relatively small budget impact), a reimbursement decision should ideally be based on hard evidence from an RCT. This is however not available.

Case series indicate that PPV is as safe as surgery.

Data from RCTs are not required to gain insight in the long term (i.e. 5 -10 years) service life of PPVs. This information will become available from ongoing registries. On the other hand, RCTs are needed to obtain hard evidence on the optimal timing and the appropriateness of PPV insertion as an alternative for the current strategy, i.e. "watchful waiting until surgery is deemed necessary". An RCT devoted to these issues would require a follow-up of many decades and may therefore be unrealistic.

If, based on these reflections, reimbursement for PPV is considered, this should be mandatory under strict conditions. This conditional reimbursement is based on the uncertainties surrounding the clinical effectiveness. The producer should in the first place be more transparent and give an explanation for the relative high price of its implant to receive this conditional reimbursement. Further, because of the necessary skills to perform this procedure, and the limited number of eligible patients, a maximum concentration of performing this procedure (i.e. restricted to 1 centre) is wishful. With this conditional reimbursement, every case should be well documented in a registry. Every year, a re-evaluation should be undertaken, to assess procedure related mortality and the short-term effectiveness of the device. As time goes by, additional long-term data will be available from dr. Bonhoeffer's and other investigators' case series.

# Scientific Summary

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# GLOSSARY

| | |
|---|---|
| ACC | American College of Cardiology |
| ACS | Acute Coronary Syndrome |
| AHA | American Heart Association |
| AMI | Acute Myocardial Infarction |
| AS | Aortic Stenosis |
| AVR | Aortic Valve Replacement |
| BACTS | Belgian Association for Cardio-Thoracic Surgery |
| BAV | Balloon Aortic Valvuloplasty |
| CABG | Coronary Artery Bypass Grafting |
| CA | Competent Authority |
| CAD | Coronary Artery Disease |
| CCOHTA | Canadian Coordinating Office for Health Technology Assessment |
| CHD | Coronary Heart Disease |
| CRD | Centre for Reviews and Dissemination |
| CVD | Cardiovascular Disease |
| ECC | extracorporeal circulation |
| EF | Ejection Fraction |
| EHS | Euro Heart Survey |
| ESC | European Society of Cardiology |
| EuroSCORE | European System for Cardiac Operative Risk Evaluation |
| FDA | Food and Drug Administration |
| HAS | Haute Autorité de Santé |
| HTA | Health Technology Assessment |
| HDE | Humanitarian Device Exemption |
| HUD | Humanitarian Use Device |
| ICER | Incremental Cost-Effectiveness Ratio |
| IDE | Investigational Device Exemption |
| IHD | Ischemic Heart Disease |
| INAHTA | International Network of Agencies for Health Technology Assessment |
| I-REVIVE | Initial Registry of EndoVascular Implantation of Valves in Europe |
| LVEF | Left Ventricular Ejection Fraction |
| MI | Myocardial Infarction |
| NB | Notified Body |
| NHS | National Health Service |
| NHSEED | National Health Service Economic Evaluation Database |
| NICE | National Institute for Health and Clinical excellence |
| NIHDI | National Institute for Health and Disability Insurance (=RIZIV/INAMI) |
| NYHA | New York Heart Association |
| PA/IVS | Pulmonary Atresia with Intact Ventricular Septum |
| PARTNER | Placement of Aortic Transcatheter Valves Trial |
| PAV | Percutaneous Aortic Valve |
| PHV | Percutaneous Heart Valve |
| PMA | Pre-market Approval |
| PPV | Percutaneous Pulmonary Valve |
| PS | Pulmonary Stenosis |
| PVT | Percutaneous Valve Technologies |
| QALY | Quality Adjusted Life Year |
| RCT | Randomised Controlled Trial |
| RECAST | Registry of Endovascular Critical Aortic Stenosis Treatment |
| RIZIV/INAMI | National Institute for Health and Disability Insurance (Rijksinstituut voor Ziekte- en Invaliditeitsverzekering/National d'Assurance Maladie-Invalidité) (=NIHDI) |

| | |
|---|---|
| RVOT | Right Ventricular Outflow Tract |
| SR | Systematic Review |
| STS | Society of Thoracic Surgeons (Score) |
| TCT | Technical Cel (Technische Cel / Cellule Technique) |
| TCI | Technical Council for Implants (=TRI/CTI) |
| ToF | Tetralogy of Fallot |
| TRI/CTI | Technical Council for Implants (Technische Raad voor Implantaten/Conseil Technique des Implants) (=TCI) |

# SCOPE

This Health Technology Assessment (HTA) report summarises current evidence supporting the use of percutaneous heart valves (PHV) in degenerative aortic valve and congenital pulmonary outflow tract disease, as compared to conservative medical therapy or traditional surgical valve replacement.

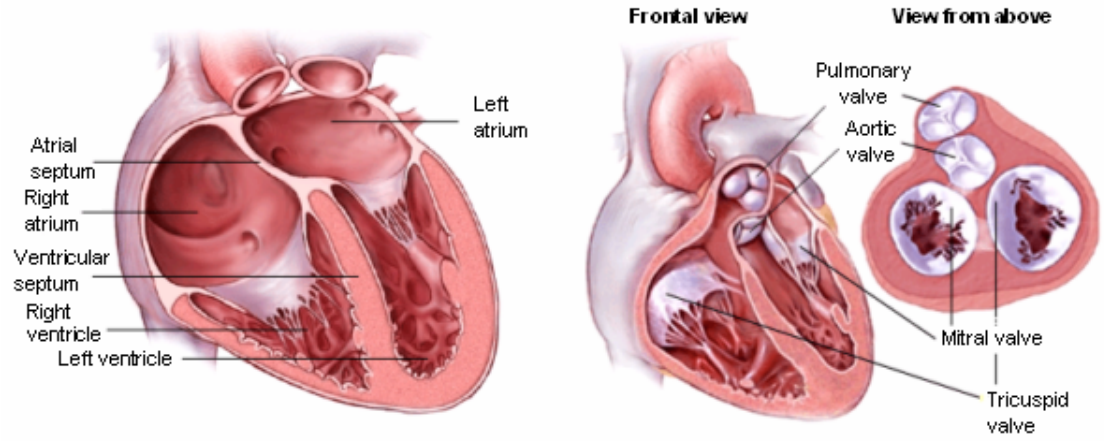
Percutaneous pulmonary valve (PPV) insertion has been first reported in the year 2000. The procedure is restricted to patients with congenital heart disease, in whom degeneration of a previously surgically reconstructed right ventricular outflow tract has occurred. Published evidence on PPV is limited to one specific valve type (Melody, Medtronic).

Percutaneous aortic valve (PAV) insertion has been reported since 2002 for the treatment of calcific aortic valve stenosis in elderly patients considered to be at unacceptably high risk for conventional surgery. Although at first, percutaneous insertion of the valve was performed transvenously, the transarterial and transapical approaches became more widespread. Currently, two different PAVs have received CE marking and are available for clinical use: the Edwards-Sapien and the CoreValve PAV.

# 1 CLINICAL BACKGROUND

The heart is composed of four chambers, two small ones - the right and the left atrium - and two larger chambers - the right and the left ventricle (Figure 1.1). The blood flow through these chambers is regulated by the heart valves. Each ventricle has two one-way valves, an inlet valve and an outlet valve. The inlet valve of the right ventricle is called the tricuspid valve (receiving blood from the right atrium) and the outlet valve is called the pulmonary valve (through which blood is pumped via the pulmonary arteries to the lungs). The inlet valve of the left ventricle is called the mitral valve (receiving blood from the left atrium) and the outlet valve is called the aortic valve (through which the blood is pumped into the aorta). Failure of any of the valves to function correctly can have significant consequences on the heart's ability to pump blood. Leaking of the valve (regurgitation), or insufficient opening of the valve (stenosis) are two disorders which can affect any of the heart valves. Sometimes both disorders can affect one valve at the same time.

**Figure 1.1: The heart chambers and valves**




Source: Centrum voor Hart- en Vaatziekten (www.chvz.be), accessed on September 12, 2008

## 1.1 AORTIC VALVE DISEASE

The aortic valve acts as a gateway for the flow of blood between the left ventricle and the aorta. During systole (the period of left ventricular contraction), the aortic valve opens and allows blood to flow from the left ventricle to the aorta towards the body. During diastole (the period of left ventricular filling) the aortic valve closes, preventing the backflow of blood to the heart, and the left ventricle is filled with blood arriving from the lungs through the left atrium across the mitral valve.[1] In patients with aortic stenosis, a narrowing of the aortic valve opening creates increased resistance to the flow of blood from the left ventricle to the aorta. This may lead to symptoms, to heart failure, and in symptomatic patients with a severe stenosis, to sudden death. In case of aortic regurgitation (also called aortic incompetence or aortic insufficiency), the aortic valve leaks every time the left ventricle relaxes, allowing blood to flow backwards from the aorta into the left ventricle. The amount of regurgitation can be quantified by echocardiography. The backflow of blood causes overloading and dilatation of the left ventricle and may lead to symptoms and to irreversible damage to the left ventricle and heart failure.

Aortic stenosis (AS) is the most common valvular heart disease and generally is degenerative in origin, resulting from a progressive age-dependent build-up of calcium. The prevalence of degenerative AS is strongly linked to the phenomenon of population ageing, and as such is expected to represent an increasingly important public health problem.[2] Rheumatic disease used to be the most frequent etiology in previous decades. In the Euro Heart Survey (EHS), of 1197 cases of aortic stenosis screened in several academic and non-academic centres from 25 countries, 82% were degenerative, 11% rheumatic and 1% due to endocarditis.

Congenital malformed aortic valves constitute an important segment of degenerated aortic valves. In a pathologic study, in half of cases, the aortic valve was bicuspid (instead of the normal tricuspid morphology).[3] Aortic stenosis constituted 44% of all valvular heart disease identified.[4] Symptoms of AS can appear when narrowing of the valve opening and subsequent overloading of the left ventricle becomes pronounced, and include angina pectoris, dyspnoea, heart failure, syncope and in some cases sudden death. The New York Heart Association (NYHA) functional scale represents a measure to assess the functional impact of the valvular dysfunction and ranges from class I, in which the patient has no limitation in daily physical activity, to class IV, in which the patient is breathless at rest.

AS can mostly be suspected clinically and diagnosis is confirmed by echocardiographic examination and doppler which enables to assess the severity of the stenosis and its consequences on the left ventricle. A valve opening area below 0.6 $cm^2/m^2$ of body surface area is a marker of severe AS. Despite its flow dependence, systolic transaortic pressure gradient is also accepted as a measure of AS severity since it is less subject to errors of measurements: a mean aortic gradient over 40–50 mm Hg indicates severe stenosis.[5-7]

Corrective treatment of AS in adults is only performed if it causes symptoms. Especially in elderly subjects, it can be difficult to ascertain if a specific symptom such as dyspnoea, fatigue or angina can be ascribed to the aortic valve disease, or whether is attributable to another cardiac or non-cardiac condition. The development of symptoms identifies a critical point in the natural history of AS.[6] Once symptoms occur, there is a sudden increase in mortality rate in the ensuing years. According to some authors, average survival after onset of symptoms is 2 to 3 years. These claims originate from work published in the late 1960s,[8] but controlled trials comparing conservative medical therapy with surgical aortic valve replacement (AVR) have never been performed. The natural history of AS nowadays and the impact of valvular correction, especially in the elderly, is not well known and may be different from the often cited historic data from Ross and Braunwald, obtained from clinical and postmortem studies, in an era when the age at the time of clinical presentation averaged 48 years and echocardiography had not yet been introduced into clinical practice.[8] In the EHS, surgery was decided against by the attending practitioner for a variety of reasons in 33% of elderly patients (≥75 yr) with severe AS. One-year survival was 90.4±2.6% in the 144 patients who had a decision to operate vs 84.8±4.8% in the 72 other in whom it was decided not to operate.[4] Other data, originating from retrospective observational studies, report a larger impact of AVR in the elderly (>80 years). In a series of 277 patients, 80 underwent AVR and 197 were treated medically. One-year, 2-year and 5-year survival rates among patients with AVR were 87, 78 and 68% respectively, compared with 52, 40 and 22% respectively in those who had no AVR.[9]

Pharmacological treatment of patients with symptomatic AS can result in a temporary alleviation of symptoms but curing AS requires surgical valve replacement with a mechanical or biological prosthesis. Mechanical heart valves are made from materials of synthetic origin like metals, whereas bioprostheses are made of materials of biological origin such as human cadaveric valves, valves from animals or valves constructed from animal tissue. The biological valvular prostheses, mostly originating from porcine or bovine tissue, have been developed with tissue preservation, together with stent designs, that contribute to preservation of anatomical characteristics and biomechanical properties of the leaflets. Bioprostheses have a risk of structural failure and need for reoperation, while mechanical prostheses have a risk of thromboembolism and anticoagulant hemorrhage. Within the bioprostheses population, younger age is a major risk factor for structural valve deterioration. Older patients (>65 years of age) have a greater risk of valve related complications with mechanical prostheses, while younger patients (<40 years of age) are at greater risk with bioprostheses.[10]

In the EHS, there was an equal proportion in the use of mechanical or bioprosthesis use, the choice being mainly driven by the age of the recipient. In current guidelines, the age threshold for choosing a mechanical valve over a bioprosthesis is 65, although in the EHS, there was a shift to 70 or 75 years.[11] AVR is the golden standard for the treatment of AS.[12]

It is a time-honoured technique which has produced excellent results in an estimated one million patients over the last four decades. Experienced surgeons can perform it with single-digit mortality, even in octogenarians.[13] Data from the EHS, show an operative (30-day) mortality rate for isolated AVR (i.e. without concomitant CABG) of 2.7% and 4.3% for AVR combined with CABG, in a population with a mean age of 64±13 years (range: 20-92).[11]

Balloon aortic valvuloplasty has been introduced in the 1980s and consists in strechting the narrowed aortic valve opening by means of an inflating balloon, in an attempt to reduce the degree of stenosis. The technique has shown to provide temporary improvement of valvular function and relief of symptoms in non-surgical population. Its use is impaired by an unacceptably high mid-term (within months) frequency of restenosis and hence, the technique has largely been abandoned.[12, 14]

### *Key points*

- **Degenerative aortic stenosis is the most common heart valve disease and its prevalence is strongly linked to population ageing.**
- **Surgical aortic valve replacement is the gold standard for the treatment of symptomatic severe AS and it can be performed safely, even in the very elderly.**

## 1.2 RIGHT VENTRICULAR OUTFLOW TRACT DISEASE

The prevalence of congenital heart disease at birth in western countries is 0.8%, indicating that in Belgium yearly about 1000 children are born with a significant heart defect. In 40% of cases no treatment is needed whereas in the remaining 60%, surgery or catheter interventions are indicated.[15] The prevalence of different congenital cardiac anomalies at birth is depicted in Table 1.1.

**Table 1.1: Prevalence at birth of specified congenital heart defects (%)**

| | |
|---|---|
| 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 |
| SUM | 100 |

Adapted from Mulder et al. Overall prevalence of congenital heart defects at birth is 0,8%.[15]

At birth, the right ventricular outflow tract (RVOT), i.e. the path the blood follows during systole from the right ventricle through the pulmonary valve to the lungs, may be severely narrowed, completely blocked or may even be absent. This occurs e.g. in pulmonary stenosis and in the setting of tetralogy of Fallot (ToF). Pulmonary stenosis can often be left untreated or, in more severe cases is corrected by balloon dilatation. In ToF, a definite repair can be performed by a single operation in 40% of cases. The remaining 60% infants require provisional repair of the anomaly early in life in order to correct blood flow to the lungs.

This life-saving intervention however commonly creates pulmonary valve incompetence for which later on, a more definitive operation is needed ("revalving"), consisting of the construction of a conduit between the right ventricle and the pulmonary artery. This type of operation can also be needed in several other rarer congenital conditions. These conduits mostly are pulmonary or aorta homograft valved, indicating that they contain a valve, harvested from a human cadaver or from a beating-heart donor.

The lifespan of homografts however is much shorter than that of the patients receiving them, due to degeneration and calcification of the valve, thereby making re-intervention later on unavoidable.[16] Moreover, the younger the recipient, the shorter the lifespan of the valve and the higher the future need for replacement because of outgrowth.[17] Actuarial freedom from explantation for degeneration is 95% at 5 and 82% at 10 years.[18] To prolong conduit lifespan and reduce the number of open heart surgeries patients need to undergo during their lifetime, stenting of the conduit has been developed. It delays conduit replacement for an average of 2.5 to 4 years.[19] Stenting is successful in dealing with stenosis in the short term, but regurgitation inevitably persists and may lead to right ventricular dysfunction.[20] In the end, most if not all patients, will during their lifetime need several follow-up operations to replace the degenerated previously implanted valve. Reoperative homograft RVOT reconstruction has been successfully done. Of 35 patients, 3 children (9%) died early postoperatively in a US series.[17] Actuarial survival and event-free curves for initial and replacement homografts were not significantly different in a series of 223 primary reconstructions and 35 redo surgeries.[17] In a Belgian series of 272 patients, aged 4 days to 69 years, in whom the RVOT was reconstructed with a homograft valved conduit, actuarial freedom from explantation for degeneration was 99.6±0.4% at 1, 94.5±1.7% at 5 and 81.8±4.1% at 10 years. 10 to 15 years after a first homograft implantation, it can be expected that 5% of patients will require a redo intervention. The survival of a second graft in 29 patients was slightly better than the first, which may at least partly be explained by the older age of patients at the time of the second homograft.[18] The replacement of a degenerated conduit is mostly performed in patients with ToF and truncus arteriosus, less frequently after a Ross operation[i].

The decision to proceed to a revalving or a redo intervention depends on clinical factors such as the presence of severe right ventricular hypertension, significant pulmonary regurgitation, right ventricular dilatation or right ventricular failure. There is no consensus on the timing of pulmonary valve implantation in this clinical situation. It is possible that if the pulmonary valve is replaced early enough, the RV dilatation and dysfunction may be reversible.[21] Other authors argue that pulmonary valve replacement should only be recommended in symptomatic patients, and may be postponed in asymptomatic subjects, even if they have severe pulmonary regurgitation.[22]

The timeline in Table 1.2 illustrates a sequence of cardiac operations encountered in a patient with ToF.

**Table 1.2: Timeline of patients with tetralogy of Fallot in whom early complete repair is not feasible (60% of cases)**

| REPAIR | INITIAL REVALVING | REPLACEMENT OF CONDUIT (REDO) | REDO | REDO |
|---|---|---|---|---|
| | | STENTING | | |
| | | PPV ? | | |
| 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 re-intervention(s) unavoidable. | | |

"PPV?" indicates conditions where percutaneous pulmonary valve (PPV) insertion may be appropriate. Ages may vary widely between patients (prof. M. Gewillig, KUL, personal communication). RVOT: right ventricular outflow tract.

[i] Performed in congenital aortic stenosis with transferring the pulmonary valve to the aortic position combined with right ventricular outflow tract reconstruction.

In order to postpone repeat surgery or to decrease the number of surgical redo interventions, and because of the limited benefit in time of pure stenting of a degenerated homograft, percutaneous valve replacement has been developed. This technology is further discussed in the current health technology assessment (HTA) report.

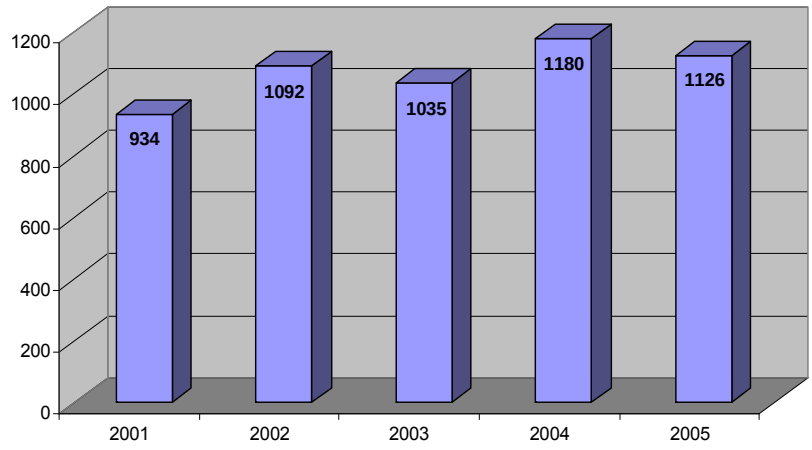
### *Key points*

- **The surgical construction of a valved conduit between the right ventricle and the pulmonary artery is needed in some types of congenital heart disease, such as tetralogy of Fallot.**
- **The lifespan of these conduits is much shorter than that of the patients receiving them, making surgical re-intervention(s) unavoidable.**
- **In order to postpone repeat surgery or to decrease the number of surgical redo interventions, percutaneous pulmonary valve replacement has been developed.**

## 1.3 CARDIAC VALVE SURGERY IN BELGIUM

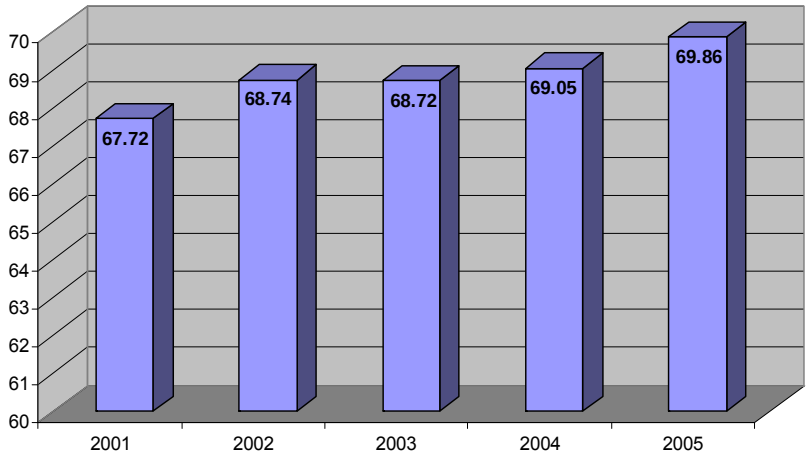
The data presented here are obtained from the cardiac surgical database report (final report 2005 - Version 26.11.2007) of the Belgian Association for Cardio-Thoracic Surgery (BACTS), that is available from the organisation's website.[23] It includes data of all 29 cardiac surgery centres in Belgium. In Belgium, yearly about 4033 isolated (i.e. not combined with other cardiac surgical interventions such as e.g. coronary artery bypass grafting - CABG) valvular operations are performed in adults. In the year 2005, 2247 of these represented monovalvular aortic valve replacements (AVR), of which about 50% were isolated AVR. Table 1.3 displays the evolution of the number of isolated aortic valve replacements in recent years. In 2005, 1015 AVR have been done in combination with another cardiac intervention, mostly a CABG.

**Table 1.3. Number of isolated surgical aortic valve replacements in Belgium from 2001 through 2005.**




Over the years, a slight increase of mean age of recipients of an aortic valve prosthesis occurred as shown in Table 1.4.

**Table 1.4. Mean age of aortic valve prosthesis recipients.**




National data on surgery for congenital heart disease are less well documented and more difficult to interpret. In contrast to aquired valvular disease, congenital anomalies represent a very wide variety of anatomical malformations. Some of these may be corrected by one single surgival intervention, whereas others require several consecutive operations.

# 2 PERCUTANEOUS HEART VALVES

## 2.1 PERCUTANEOUS AORTIC VALVE (PAV)

The idea of the percutaneous insertion of an aortic valve resulted from the disappointing results of the percutaneous balloon aortic valvuloplasty (BAV) that was introduced in 1986, and gave rise to a high early rate of restenosis.[24] BAV had been developed in an attempt to help patients with AS, who were severely symptomatic but considered inoperable. The operability of patients is based on clinical judgement, supplemented with information obtained from operative risk scores derived from historic data on patients that underwent cardiac surgery.[4] High risk indicators include advanced age, severe chronic obstructive pulmonary disease, severely reduced left ventricular function, advanced renal or liver failure, diabetes mellitus, and recurrent neurologic insults.

Although it reflects only a limited number of surgical risk factors, the EuroSCORE (European System for Cardiac Operative Risk Evaluation) risk score is commonly referred to in papers related to PAV insertion. It was introduced in 1999 to predict surgery related mortality risk.[25] This risk model is used for any cardiac surgery, and is not specifically designed for aortic stenosis.[13] Both a simple additive and a logistic model have been established and validated (Figure 8.1). For a given patient, the EuroSCORE reflects the predicted operative mortality, although for patients considered at the highest risk, the EuroSCORE may overestimate the surgical risk.[26, 27] This has been confirmed in a recently published evaluation in a surgical series from the Mayo Clinic where an estimated 30-day mortality of 23.6% sharply contrasted with an observed mortality of 5.8%. [28] Because there is evidence that actual outcomes have improved, an update of the model is in preparation ("EuroSCORE 2008") to better reflect contemporary practice.[ii]

The concept of percutaneous insertion of a cardiac valve was first applied to the pulmonary valve, because this valve is more easily reached and tolerates less than perfect results better than the aortic valve.[12] The first human percutaneous aortic valve implant has been performed by Cribier in April 2002.[29] Initially, PAV insertion was completed via the antegrade approach, indicating that the delivery catheter and the PAV are advanced along the direction of blood flow. After puncture of the femoral vein, the catheter is advanced to the right atrium and following puncture of the interatrial septum, the device is advanced via the left atrium through the mitral valve opening. In this way, positioning and deployment of the PAV assembly occurs across the ventricular surface of the aortic valve which is usually less calcified, resulting in a smoother passage.[24] Because of the demanding nature of the procedure, and the potential complications at the level of the mitral valve induced by the transseptal catheters, the antegrade (transvenous) approach of the aortic valve has been mostly replaced by the retrograde (transarterial) approach, which will be described in more detail in the next section. This technique however can be hampered due to difficulties to advance large catheters through tortuous and diffusely diseased femoral and iliac arteries, often encountered in elderly people. These difficulties have led to the development of the transapical approach where the same device is introduced from the cardiac apex via a mini-thoracotomy. Due to this selection process, patients treated by the transapical route mostly have a higher risk profile than patients treated by the transarterial approach. The feasibility of PAV insertion not only depends on the vascular accessibility of the aorta, but is also dependent on anatomic characteristics related to the ascending aorta and the aortic annulus. Correct sizing of the valve is critical to minimize the potential for paravalvular leakage and to avoid prosthesis migration after placement.[7] Some currently accepted contra-indications for PAV are (congenital) bicuspid valves because of the risk of incomplete deployment of the prosthesis and the presence of asymmetric heavy valvular calcification, which may compress the coronary arteries during PAV insertion.[7] Other contra-indications, related to a specific type of PAV will be discussed in the corresponding sections.

[ii] http://www.euroscore.org/

In 2008, a position statement, originating from the European Association of Cardio-Thoracic Surgery (EACTS) and the European Society of Cardiology (ESC), in collaboration with the European Association of Percutaneous Cardiovascular Interventions (EAPCI) on PAV implantation for patients with AS has been published.[2] Based on analysis of available data and personal experience by the authors, it was concluded that the technique is feasible and provides hemodynamic and clinical improvement for up to 2 years in patients with severe symptomatic AS at high risk or with contraindications for surgery. It was highlighted that questions remain concerning safety and long-term durability. The committee of experts recommend that the use of PAV should be restricted to high-risk patients or those with contraindications for surgery and that careful evaluation is needed to avoid the risk of uncontrolled diffusion of the technique.

A scientific statement from the American Heart Association (AHA) on several minimally invasive valve procedures was also published recently.[30] It is emphasized that PAV technology is still in its infancy. The technique requires specific skills from the part of the interventionalist and the committee contends that, even after FDA approval, percutaneous valve devices (in general) should be used in only a small number of centres with excellent surgical and catheter experience until they are thoroughly tested in the clinical arena. The experts also warn against extrapolating data obtained in high-risk subjects to lower-risk populations, given the outstanding track record achieved by surgical AVR.

Since Cribier's first experiences, several devices have been developed and at least 20 types are currently being tested at various stages in humans, in animal models or in laboratories.[31] Currently, two different PAVs have received CE marking and are available for investigational purposes and clinical use: the Edwards and the CoreValve PAV. This HTA report on PAV is limited to the study of these PAV types.

### 2.1.1 The Edwards PAV

The first PAVs for human application were manufactured by Percutaneous Valve Technologies (PVT), Fort Lee, NJ, USA. Protoypes were tested in a sheep model and the first human implant was performed in 2002.[29] The acquisition of Percutaneous Valve Technologies by Edwards LifeSciences in 2004, led to further modifications of the valve "(Cribier-Edwards" and "Edwards-Sapien") and its implantation instruments. Whereas the initial prosthesis developed by Cribier was made of equine pericardium ("Cribier-PVT" and "Cribier-Edwards"), the currently used Edwards PAV, known as the "Edwards-Sapien" valve, is a tri-leaflet bioprosthesis that is made of bovine pericardium and is integrated into a stainless steel, balloon expandable stent frame. The prosthetic stent valve is delivered by the manufacturer in the expanded state and has to be mechanically crimped on a balloon catheter immediately before implantation.[32] The "Edwards-Sapien" PAVs are currently available in two different dimensions with a maximal expansion of 23 and 26 mm (Figure 2.1), that can be advanced trough a 22F[iii] or a 24F percutaneous sheath. The suitability for PAV obviously depends on the vascular accessibility and can be rendered impossible due to severe iliofemoral arterial disease. It is also restricted by aortic annulus dimensions; these are measured echocardiographically and should be more than 18 mm and less than 26 mm.[32]

[iii] The "French" (F) catheter scale is used to measure the outer diameter of catheters. The diameter in millimeters of the catheter can be determined by dividing the French size by 3.

**Figure 2.1: The Edwards Sapien Transcatheter Heat Valve (Edwards Lifesciences) (side and top view)**

Source: pictures received from Edwards

During the first years following the introduction of the technique, the antegrade approach via the interatrial septum was used for PAV implantation, as discussed earlier. Hereby, catheterization through the interatrial septum is performed from the femoral vein. A flotation balloon catheter is used for antegrade crossing of the aortic valve, and a guide wire is advanced through this catheter to the descending aorta. After predilatation of the native aortic valve with a balloon catheter, the PAV is advanced over the wire, across the interatrial septum, and within the stenotic native valve. To improve the precision of PAV implantation, rapid cardiac pacing (180 to 220 beats/min) of the heart up to 10 seconds decreases aortic blood flow and prevents PAV migration during balloon inflation.[14] The disadvantage of this antegrade technique is that it is complex and technically demanding. Moreover, there is a risk of damage to the mitral valve which has led to a renewed interest of the retrograde technique which is similar to the routine BAV.[24] Here, the aortic valve is reached straight against the direction of blood flow via the ilio-femoral arteries and the descending aorta, and a guidewire is advanced through the aortic valve orifice. After predilatation of the native aortic valve, the PAV is advanced over a guidewire within the native valve and deployed as in the antegrade technique. The antegrade approach of the aortic valve has been mostly replaced by the retrograde approach. The retrograde technique however can be hampered due to difficulties to advance large catheters through tortuous and diffusely diseased femoral and iliac arteries, often encountered in elderly people. These difficulties have led to the development of the transapical approach where the same device is introduced from the cardiac apex, directly into the left ventricle via a mini-thoracotomy, with or without femoral extracorporeal circulation.[33] As in the transvascular approach, valvuloplasty is performed first, after which a 33F or 26F delivery sheath is advanced through the left ventricular apex to insert the PAV under fluoroscopic imaging.[34] At the end of the procedure, the apex is closed surgically with purse-string sutures. The pericardium is closed over the apex and a left lateral chest tube is inserted.

The first results of single-centre feasibility series, using the Cribier-PVT valve mostly via the antegrade approach, were published in 2004[14] and 2006[35]. After the acquisition of Percutaneous Valve Technologies by Edwards LifeSciences in 2004, there have been continued technical improvements of the system and in the protocol for device delivery, in order to better traverse the vascular system and the aortic arch. Moreover, a larger caliber PAV was developed, because of the concern of valve migration and residual paravalvular leaks. For regulatory reasons (sic), these technologic advances could not be used in France before 2006 and were evaluated initially by J. Webb in Vancouver, Canada and later on in the US.[36] The antegrade and retrograde procedures have been performed both under local or general anesthesia.

The transapical approach, including a mini-thoracotomy, obviously requires general anesthesia. Dual antiplatelet therapy is instituted at least 24 hours before the procedure with aspirin and clopidogrel.[24] To date, reportedly more than 1000 Edwards PAVs have been implanted worldwide in humans, using one of these different approaches.[36]

### 2.1.2 The CoreValve PAV

The CoreValve PAV consists of a trileaflet bioprosthetic porcine pericardial tissue valve that is mounted and sutured in a self-expanding nitinol stent (Figure 2.2). In contrast to the Edwards type of PAV, which is deployed by means of a balloon, the stent of the CoreValve is self-expandable and is contained within a sheath from which it is pushed once adequate positioning of the device within the native aortic valve is accomplished. The inner diameter of the valve is 21 mm. The lower portion of the prosthesis has high radial force to expand and exclude the calcified leaflets and to avoid recoil; the middle portion carries the valve and is constrained to avoid the coronary arteries; and the upper portion is flared to fixate the stent in the ascending aorta and to provide longitudinal stability.

**Figure 2.2: The aortic bioprothesis of the CoreValve Revalving System (Corevalve)**


Source: Received from Corevalve with permission to use for this report (October 23, 2008)

The original device underwent several improvements. The first-generation device used bovine pericardial tissue and was constrained within a 24F delivery sheath. The second-generation device incorporated a porcine pericardial tissue valve within a 21F sheath, whereas third generation valves are delivered in an 18F sheath, the reduced profile allowing access through smaller-diameter vascular beds.[37, 38] The CoreValve is designed for a retrograde arterial approach and vascular access is obtained either with or without standard surgical cutdown of the common iliac artery, the common femoral artery, or the subclavian artery. A transapical approach as used for the insertion of the Edwards PAV has also been reported for the CoreValve recently. The morphological suitability depends on aortic annulus dimensions that should be more than 20 mm and less than 27 mm.[37] The procedure can be performed with the patient under general anesthesia or with local anesthesia in combination with a mild systemic sedative/analgesic treatment. The type of hemodynamic support (extracorporeal percutaneous femoro-femoral bypass, tandem heart, extracorporeal membrane oxygenation, or none) is dependent on the operator. Balloon valvuloplasty is performed first under rapid pacing, after which the device is deployed retrogradely over a stiff guidewire under fluoroscopic guidance.[37] Aspirin is administered before the procedure and continued indefinitely. In addition, all patients receive clopidogrel (300-mg loading dose), followed by 75 mg daily for at least 6 to 12 months. During the intervention, the patient receives weight-adjusted intravenous heparin. To date, reportedly more than 1400 CoreValve PAVs have been implanted worldwide in humans, using one of these different approaches (Séguin, personal communication, August 7, 2008).

### *Key points*

- **The Edwards-Sapien PAV, is a bioprosthesis that is made of bovine pericardium and is integrated into a stainless steel, balloon expandable, stent frame. Although it was initially intented for use via the antegrade venous approach, the retrograde transarterial and the transapical approach have become more common. Up to now, more than 1000 Edwards PAVs have been implanted worldwide.**
- **The CoreValve PAV consists of a bioprosthetic porcine pericardial tissue valve that is mounted and sutured in a self-expanding nitinol stent. It is designed for a retrograde arterial approach. Devices for transapical delivery have been introduced recently. To date, more than 1400 CoreValve PAVs have been implanted worldwide.**
- **The suitability for PAV is dependent on aortic annulus dimensions. Iliofemoral arterial disease may preclude the transarterial approach for PAV insertion.**

## 2.2 PERCUTANEOUS PULMONARY VALVE (PPV)

Because of the significant morbidity and mortality burden imposed by repeated cardiac surgery in patients in whom a RVOT valved conduit has been constructed, percutaneous dilatation and stenting of degenerated conduits has emerged as a technique for delaying surgical replacement. Besides relieving the obstruction to blood flow, stenting creates valve regurgitation which is initially generally well tolerated by patients. As time goes by, however, pulmonary regurgitation increases susceptibility to arrhythmias, sudden death and right ventricular dysfunction, making implantation of a valve within the conduit inescapable. In order to overcome the shortcomings of percutaneous dilatation, yet postponing redo-surgery, the percutaneous pulmonary valve (PPV) has been developed, in an attempt to reduce the number of operations needed over the total lifetime of these patients.

Up to now, the Medtronic Melody PPV has been best studied and documented in clinical practice. It concists of a segment of a bovine jugular vein, with a thinned down venous wall having a central competent venous valve. This valve is attached to a platinum/iridium stent with a length of 28 mm and a diameter of 18 mm, which can be crimped to a size of 6 mm and re-expanded to 22 mm. The valve is implanted via a catheter delivery system with a 22 French crossing profile.[iv] Published evidence on PPV is essentially limited to a single operator and relates to one specific valve type (Melody, Medtronic) (Figure 2.3).

Because of vascular dimensions needed to percutaneously introduce the device, the technique cannot be used in the very young, and patients have to weigh at least 20 kg.[39] The technique of PPV insertion is similar to that of the percutaneous dilatation and stenting of the native pulmonary valve as performed in congenital pulmonary stenosis, and is familiar to interventional pediatric cardiologists. The procedure is performed under general anesthesia and requires standard right heart catheterisation techniques, usually from a femoral vein. Because compression of coronary arteries by the device has been described, angiography of the ascending aorta or coronary angiography is performed to assess coronary arteries morphology.

The morphological suitability for PPV is assessed by measuring the RVOT using computerized tomography, magnetic resonance imaging or angiography and in some patients by invasive balloon sizing. RVOT dimensions have to be less than 22 x 22 mm and more than 14 x 14 mm.[40] PPV insertion has been first reported in the year 2000. The technique has since then been improved. Published experience with the PPV is essentially limited to a single operator and relates to the Melody PPV, manufactured by Medtronic. Investigators from 17 European centres have reportedly acquired experience with the device in 399 patients, of which 10 were treated in one Belgian centre. Until May 2008, 556 Melody PPVs had been implanted worldwide.[41]

[iv] Data provided by Medtronic, August 2008.

**Figure 2.3: The Melody™ Valve and Ensemble System (Medtronic)**

Source: http://wwwp.medtronic.com/newsroom/content/1189782189248.high_resolution.jpg and http://wwwp.medtronic.com/newsroom/content/1159976398868.jpg (accessed September 3, 2008)

### *Key points*

- **Published evidence on PPV is essentially limited to a single operator (P. Bonhoeffer) and relates to one specific valve type (Melody, Medtronic).**
- **From a technical point of view, percutaneous pulmonary valve (PPV) insertion is similar to native pulmonary valve stenting, a technique that is familiar to interventional pediatric cardiologists.**
- **Standard right heart catheterisation is supplemented by coronary artery imaging in order to prevent coronary artery compression by the device.**
- **Eligibility for PPV is dependent upon the dimensions of a previously constructed RVOT conduit. Patients have to weigh at least 20 kg.**

## 2.3 REGULATORY STATUS

### 2.3.1 EU vs. US

According to the European directive on medical devices (annex IX directive 92/42/ECC) implantable devices can be defined as any device which is intended to be totally introduced into the human body or to replace an epithelial surface or the surface of the eye by surgical intervention and which is intended to remain in place after the procedure. Any device intended to be partially introduced into the human body through surgical intervention and intended to remain in place after the procedure for at least 30 days is also considered an implantable device.[42] The regulation of medical devices in Europe was introduced in 1991 with the Medical Devices Directive. Medical devices are classified in four classes: class I (low risk), II a (medium risk), II b (elevated risk) and III (high risk) according to the risk linked to the device. The higher the classification, the more elaborate the level of the required assessment will be. Cardiac devices are placed in class III.[43]. In this class, a CE mark for marketing can only be affixed by the manufacturer after approval of the "Design Dossier" by a Notified Body (NB), designated by a Competent Authority (CA).

The CE mark denotes a formal statement by the manufacturer of compliance with the directives' requirements. The Medtronic Melody PPV received CE marking in October 2006. The CoreValve PAV received CE marking in May 2007 while the Edwards Sapien PAV has been granted a CE marking in September 2007 for its transfemoral device and in December 2007 for its transapical device. Product commercialisation for the transfemoral approach of the Edward Sapien PAV was initiated in October 2007 and for the transapical approach in January 2008.[v]

[v] Information provided by Edwards Lifesciences, June 2008.

Unlike the pharmaceutical sector, where new drugs have to undergo series of regulatory clinical trials during development, the evaluation and timing of health technologies such as medical devices is less demarcated. For instance, no pre-market clinical trials are required for obtaining "CE marking" of medical devices.[42] The regulation of medical devices is different in the US as compared to the European Union. The most remarkable difference with EU countries is the requirements for placing devices on the market. As in the EU, in the US medical devices are classified into classes depending on the intended use of the device, indications for use, and risk. In the US there are three classes for which regulatory control increases from Class I to Class III. Most Class I devices are exempt from Pre-market Notification 510(k); most Class II devices require Pre-market Notification 510(k); and most Class III devices require Pre-market Approval (PMA). An investigational device exemption (IDE) can be provided to allow the investigational device to be used in a clinical study in order to collect safety and effectiveness data required to support a PMA application or a Pre-market Notification (510(k)) submission to FDA. The 510(k) is a pre-marketing submission made to FDA to demonstrate that the device to be marketed is as safe and effective to a legally marketed device that is not subject to PMA. In contrast with the EU system FDA's PMA requires the demonstration of a medical device's clinical effectiveness as a precondition for marketing. This is not the case with CE marking.[42]

The technical CE label does by no means provide evidence for the clinical effectiveness nor the clinical safety and potential long term adverse events in the patient populations concerned. For class III implants clinical data on conformity with the 'essential requirements' (i.e. characteristics and performance of the device) or the justification why clinical data are not necessary, is required. This requirement is part of the assessment of the technical file by the notified bodies. It is unclear by which methodology these clinical data are critically appraised. Several implants and invasive devices easily obtained their CE label in the past, while there were at most ongoing clinical trials. For some devices, only several years later the first trials were published, possibly not showing clear clinical benefits.[vi] This highly questions the extent and the rigour of the CE labelling process. It can be regarded as a necessary first step to guarantee technical safety and good manufacturing of a device, but its value in health technology assessment for health insurance is limited.[42]

In the US, an exemption on the effectiveness requirements is possible for Humanitarian Use Device (HUD). A HUD is 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. FDA may authorize a company to market their HUD by approving a Humanitarian Device Exemption (HDE), which is similar to a pre-market approval (PMA) application, but exempt from the effectiveness requirements. [vii] Reasonable evidence of safety and only probability of benefit are required for this exemption.[43]

### 2.3.2 Ongoing studies

The FDA has placed PHV in class III, the highest risk class for devices, exhibiting the most serious consequences to patients in case of device failure. Pre-market approval for these devices in the US require scientific evidence for safety and effectiveness, after reasonable assurance of feasibility and preliminary safety has been demonstrated.[43]

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vi 'In Belgium for example, aortic endovascular devices were reimbursed by social security during several years in seventy hospitals outside a clinical trial setting. Endovascular stentgrafts were used to repair abdominal aorta aneurysms (EVAR). The rationale behind EVAR is to offer an alternative for otherwise inoperable patients and to reduce the severe postoperative mortality and morbidity of open repair, speed up recovery, and reduce costs through decreased length of stay in hospital and intensive care. Later on, clinical trials in other countries demonstrated that this technique offered only limited added (clinical) value, depending on the patient population.[44-50]. Several of the EVAR devices were withdrawn from the market in the past decade. Furthermore, there were elaborate discussions in the Belgian health insurance bodies on the reimbursement of carotid stenting. These stents are already being used in several Belgian hospitals outside a randomized clinical trial (RCT) setting. The SPACE and EVA-3S trials were halted early for reasons of safety and futility.[51, 52] In both trials, there were more strokes and higher mortality than in the control group with carotid endarterectomy.' (from Vinck et al.[53])

vii http://www.fda.gov/cdrh/ode/guidance/1381.html#f1 (accessed September 15, 2008)

This has been accomplished by the published feasibility studies that will be discussed later. They led to granting an IDE to a currently ongoing pivotal randomised controlled trial (RCT), the PARTNER (Placement of AoRTic TraNscathetER Valve Trial) trial. This trial should be distinguished from the "PARTNER EU" study that is a single arm, prospective post-market registry, conducted in 9 centres in 6 EU countries (including 1 Belgian centre: Aalst, OLV Ziekenhuis). Patient enrollment was initiated in April 2007 and completed on January 31, 2008. 130 patients were included and both transfemoral or transapical PAV insertions were accepted.[54] First outcome data presentations are planned for the fall of 2008.[viii] To avoid ambiguity, the United States based RCT often is referred to as the "PARTNER US" or the "PARTNER IDE" trial.

ClinicalTrials.gov was searched (September 15, 2008) for studies related to the Corevalve Revalving PAV system and the Medtronic Melody PPV system.

No studies were found for Corevalve. For Melody, the Melody TPV Post-Market Surveillance Study was started in October 2007, and is currently recruiting patients with dysfunctional RVOT conduits. It is a non-randomised, prospective, interventional observational multi-centre study, designed to assess the long-term clinical performance of the Melody PPV in the post market environment over a period of five years after transcatheter implantation. In addition, the quality of life of implanted subjects will be assessed over five years. About 60 patients would be included. The estimated study completion date is august 2014.[ix]

In the US, the HUD-label was assigned for the Melody PPV for "use in patients with the following clinical conditions: 1) Patients with regurgitant prosthetic RVOT conduits with a clinical indication for invasive or surgical intervention, OR, 2) Patients with stenotic prosthetic RVOT conduits where the risk of worsening regurgitation is a relative contraindication to balloon dilatation or stenting, and 3) Existence of a full (circumferential) RVOT conduit that was equal to or greater than 16 mm in diameter when originally implanted."[x] Medtronic submitted a request for HDE on August 28, 2008 (personal communication). The procedure currently is still running.

### 2.3.3 Conditional reimbursement of medical devices in Belgium

Procedures for the evaluation and reimbursement of medical devices were described in a previous KCE report from which we copied some parts with respect to "article 35" of the medical nomenclature.[42] This article distinguishes 5 categories of implants: category 1 being the active implants, category 2 being the high risk implants, category 3 being the medium or low risk implants, category 4, the custom made implants. Category 5 concerns implants for limited clinical use or new implants for which the Technical Council for implants (TRI/CTI) decides that an evaluation is necessary. Category 5 relates to each implant that is intended to be used in an appropriate clinical human environment during a specific period of evaluation and/or to be used for a specific indication. It encompasses

- A new or a slightly modified version of an implant of category 1 or 2 figuring on the limitative lists for an accepted indication, or an implant figuring on the limitative list but used for a new indication; or
- An entirely new implant for which the "Technical Council for Implants" (TRI/CTI) considers that a period for evaluation of the reimbursement is necessary.

According to the category of the implant, there are different conditions for reimbursement and surcharges for the patient. For category 5, requests for reimbursement are introduced to the TRI/CTI (Figure 2.4). The TRI/CTI proposes the modalities of the evaluation, the criteria for reimbursement and the amount of reimbursement by social security. It transmits this proposition to the "Commission for Conventions between the hospitals and sickness funds" (OI/CCI).

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viii Information provided by Edwards Lifesciences, June 2008.

ix http://clinicaltrials.gov/ct2/show/NCT00688571?term=Melody&rank=1 (accessed September 15, 2008)

x Department of Health & Human Services, Public Health Service, USA. Office of Orphan Products Development. Humanitarian use device designation request #07-0180. July 10, 2007.

The OI/CCI advises on the proposition and transfers its advice for approval to the "Insurance Committee". The proposition contains a proposition of a convention with scientific societies, physicians or hospitals. It determines the conditions for reimbursement:

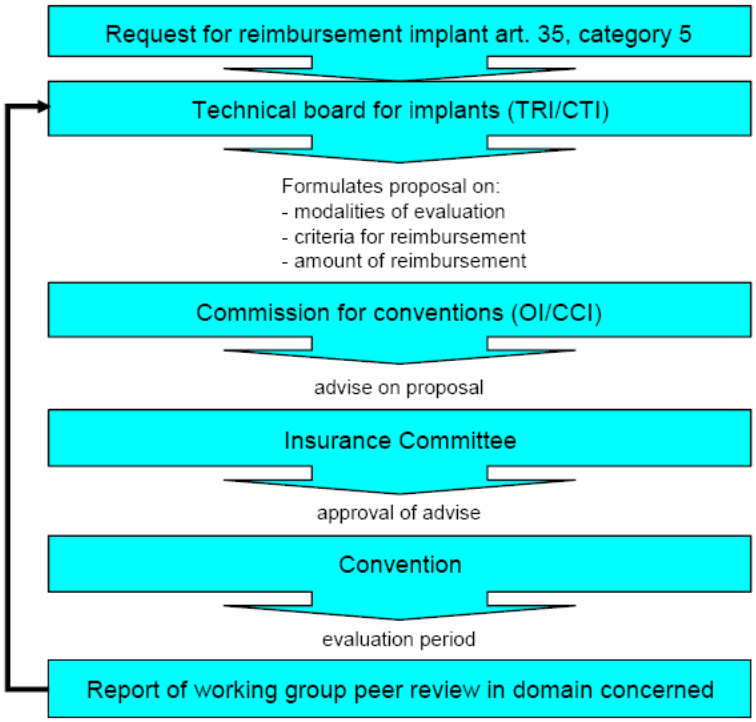
- the target group and the criteria of inclusion of the patients are defined
- an evaluation period is scheduled
- norms aimed for the implantation centres/physicians are set
- the number of implants or patients is (can be) limited
- the feedback between the physicians and the system is compulsory in order to be reimbursed
- the reimbursement and the evaluation are specified
- the evaluation method is described
- the reimbursement procedure is clearly defined. Mostly, the "College of physician-directors" (CGD/CMD) is charged with the examination of the individuals file.

Before the end of the agreed period of evaluation, the peer review group competent in the domain at stake should present a report based on the collected data and the scientific literature on behalf of the TRI/CTI and the CGD/CMD. The report also contains a proposition for a permanent reimbursement regulation.

This proposition is then transmitted with the advice of the CGD/CMD to the TRI/CTI, who works out, in case of a favourable evaluation, the proposition into a full reimbursement regulation. It transmits its proposition to the OI/CCI.

The OI/CCI advises on the proposition and submits its advice to the "Insurance Committee" for approval.

**Figure 2.4: Current procedure for reimbursement of implants (Art. 35, §3, cat. 5 medical nomenclature)**



### *Key points*

- **In Europe, no efficacy or effectiveness prerequisites are needed for marketing approval. Solely the assessment of technical safety of the device and the quality of the manufacturing process is demanded.**
- **The technical CE label does by no means provide evidence for the clinical effectiveness nor the clinical safety or the potential for long term adverse events.**
- **In contrast, in the US, pre-market approval for class II and III devices requires scientific evidence for safety and effectiveness, after reasonable assurance of feasibility and preliminary safety have been demonstrated.**
- **In the US, an investigational device exemption (IDE) can be provided to allow the investigational device to be used in a clinical study in order to collect safety and effectiveness data.**
- **An IDE was granted for the Edwards-Sapien PAV for use within the PARTNER-US randomised trial.**
- **In the US, a "humanitarian use device" (i.e. indicated in <4,000 US cases per year), can be granted a Humanitarian Device Exemption (HDE) for marketing, which is similar to a pre-market approval application with exemption from the effectiveness requirements.**
- **In Belgium, an implant for which the Technical Council for Implants (TRI/CTI) considers that a period for evaluation of the reimbursement is necessary, can be conditionally reimbursed.**

# 3 CLINICAL EFFECTIVENESS

## 3.1 LITERATURE SEARCH

### 3.1.1 Search strategy and eligibility

#### *3.1.1.1 Health technology assessments*

In order to find previously published HTA reports we started our search on May 9, 2008 by consulting the database of CRD (Centre for Reviews and Dissemination), making use of two MeSH terms: (1) "heart valve prosthesis" and (2) "heart valve prosthesis implantation". This resulted in 20 and 19 hits respectively of which 4 and 0 reports were selected based on title. From these, we eventually selected 1 HTA report for full text appraisal: "Emerging Technology List", published in June 2005 by the Canadian CCOHTA (Canadian Coordinating Office for Health Technology Assessment) and briefly covering **PPV and PAV**.[55]

Searching the INAHTA (International Network of Agencies for Health Technology Assessment) database revealed two additional reports covering **PAV**, both published in 2008: one from the French HAS (Haute Autorité de Santé), published in January 2008,[56] and one from Austria, published on February 4, 2008. NICE (National Institute for Health and Clinical excellence) published an HTA on PAV on February 25, 2008. Hand-searching further revealed a "Horizon Scanning Technology Prioritising Summary" published by the Australian and New Zealand Horizon Scanning Network in February 2007 and updated in August 2007.[57] Because of its less formal nature and being less up to date, we did not include the latter, leaving three 2008 HTA reports on PAV for further discussion.

We retrieved two HTA reports on **PPV**: one originating from NICE ("Interventional procedure overview")[58] and one systematic review from Austria, published in March 2008.[59]

#### *3.1.1.2 Primary studies and systematic reviews*

Searching the database of CRD and the Cochrane database revealed no systematic reviews on PHV.

On June 23, 2008, we performed a Medline search via PubMed, starting our search from Jan 1, 2000 on, because the first reports on PHV were published in 2000. The MeSH terms "Heart Valve Prosthesis" and "Heart Valve Prosthesis Implantation" were extended with text words and MeSH terms related to aortic or pulmonary valve disease. We used the following search string:

(((percutaneous OR transcutaneous OR transcatheter OR transapical OR trans apical OR trans catheter OR cribier OR corevalve)) AND (("Heart Valve Prosthesis"[Mesh] OR "Heart Valve Prosthesis Implantation"[Mesh])) AND ((("Aortic Valve"[Mesh] OR "Aortic Valve Stenosis"[Mesh] OR "Aortic Valve Insufficiency"[Mesh])) OR (("Pulmonary Valve"[Mesh] OR "Pulmonary Valve Insufficiency"[Mesh] OR "Pulmonary Valve Stenosis"[Mesh]))) AND (("2000/01/01"[EDat] : "3000"[EDat])) This resulted in 215 hits.

On June 19, 2008, we performed an EMBASE search, again starting from Jan 1, 2000 on. The following search string was used: 'heart valve prosthesis'/exp AND (percutaneous OR transcutaneous OR transapical OR 'trans AND apical' OR transcatheter OR 'trans AND catheter' OR cribier OR corevalve) AND [2000-2008]/py. This resulted in 63 hits.

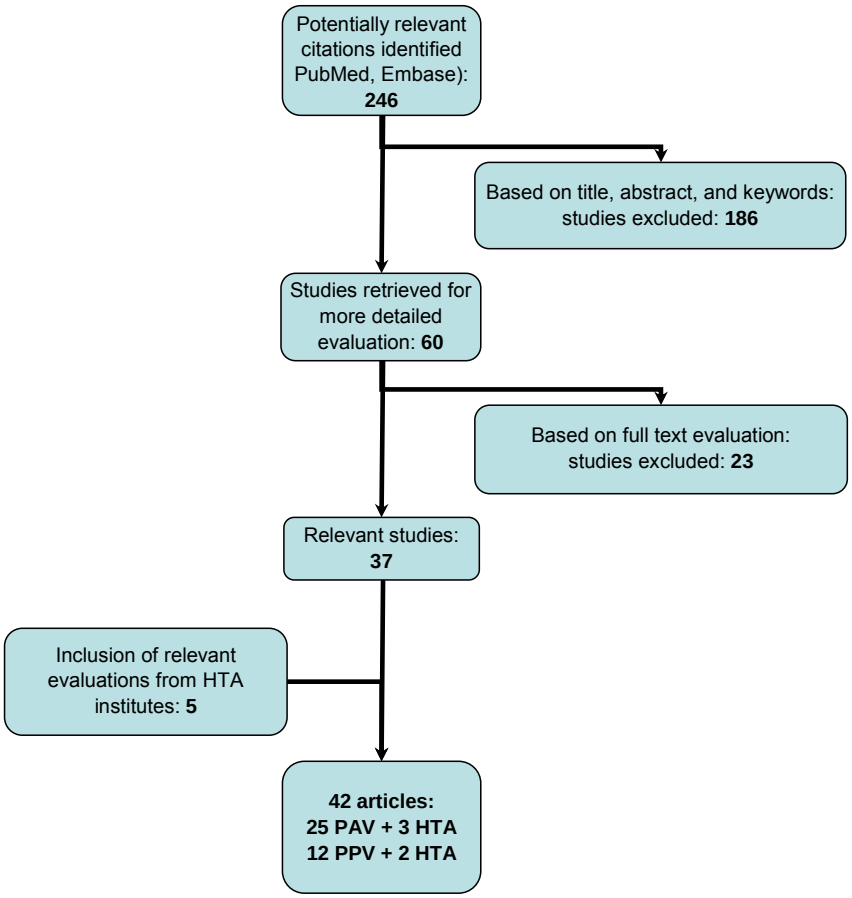
On July 28, 2008, an update of the PubMed search described above was repeated and resulted in one additional case series on transapical aortic valve insertion.[34]

Combining these searches and eliminating duplicates resulted in 246 articles. Based on title and abstract 186 articles were rejected and 60 full text papers were studied.

Of these, 23 were rejected because they did not report PHV cases, because devices beyond the scope of this report (Edwards, CoreValve, Melody) were used, because of lack of adequate clinical data, or because only physiological aspects of PHV were addressed. Of the 37 articles thus retrieved, 25 were related to PAV and 12 to PPV technology. A flow-chart depicting the selection procedure for relevant papers is shown in Figure 3.1.

Two papers that were not yet indexed by Medline when we performed our literature search, but became published in June 2008, were later added to this literature review.[26, 60] Data presented at meetings, those provided by manufacturers and information retrieved from grey literature have not been included in our formal literature survey because of the non peer-reviewed character of the data.

**Figure 3.1. Literature search decision tree.**




## 3.1.2 Data extraction

No randomised controlled trials on PHV have been published so far. All papers retrieved were case series. Of 25 reports on PAV, 9 were "single case" reports and of 12 articles on PPV, 4 were "single case" reports. Because of their obvious anecdotal nature, these "single cases" will only be mentioned further on when considered appropriate.

The following data were extracted from each study: valve type (Edwards, CoreValve, Melody), study centre, number of patients, demographics, clinical data on patients and specifications of the valve disease, port of entry (arterial or venous), diameter of the introducing device needed, technical succes rate, complications, follow-up data, and surgical aortic valve replacement after (attempted) percutaneous approach.

## 3.2 LITERATURE REVIEW – PERCUTANEOUS AORTIC VALVE

### 3.2.1 Health technology assessments

Three HTAs, all published in 2008, were selected for further discussion.[56, 61, 62] Table 3.1 in the first column enlists the case series retrieved for discussion in the current report, and indicates in the right columns whether they were incorporated in these three international 2008 HTA reports. The most relevant article that was not yet included in any previous HTA, is the case series by Svensson, that incorporated 40 patients, treated between December 2006 and February 2008 with a transapical inserted Edwards PAV.[34]

**Table 3.1. HTA reports published in 2008 and the corresponding case series they included.**

| REFERENCE | STUDY CENTRE | PAV TYPE | n | 2008 HTA reports | | |
|---|---|---|---|---|---|---|
| | | | | NICE | HAS | Austria |
| **ROUEN SERIES, antegrade** | | | | | | |
| Cribier[14] | Rouen, France | Edwards | 6 | X | X | X |
| Cribier[35] | Rouen, France | Edwards | 36 | X | X | X |
| Eltchaninoff[31] | Rouen, France | Edwards | 36 | - | - | - |
| Sack[63] | Essen, Germany | Edwards | 2 | - | - | - |
| **VANCOUVER SERIES, retrograde** | | | | | | |
| Webb[64] | Vancouver, Canada | Edwards | 18 | X | X | X |
| Webb[32] | Vancouver, Canada | Edwards | 50 | X | X | X |
| **APICAL APPROACH** | | | | | | |
| Lichtenstein[65] | Vancouver, Canada | Edwards | 7 | X | X | X |
| Ye[66] | Vancouver, Canada | Edwards | 7 | X | X | - |
| Walther[33] | Leipzig, Germany | Edwards | 30 | X | X | - |
| Walther[67] | Leipzig, Germany | Edwards | 59 | X | X | - |
| Svensson[34] | Multicentre, US | Edwards | 40 | - | - | - |
| **COREVALVE** | | | | | | |
| Grube[38] | Siegburg, Germany | CoreValve | 25 | X | X | X |
| Grube[37] | Siegburg, Leipzig, Montreal | CoreValve | 86 | X | X | X |
| Marcheix[68] | Montreal, Canada | CoreValve | 10 | - | - | X |
| Berry[69] | Montreal, Canada | CoreValve | 11 | X | X | X |

Listing of articles retrieved for discussion in this HTA report. An X indicates whether a 2008 HTA report incorporated the corresponding case series. n represents the number of patients included in the series.

#### *3.2.1.1 U.K.: NICE*

This report from NICE is not a formal HTA, but a so-called "Interventional Procedure Overview" prepared in December 2007. It is based on a rapid review of the medical literature (search until Nov 13, 2007) (Table 3.1) and specialist opinion and should not be regarded as a definitive assessment of the procedure.[70] It has rather been prepared to assist members of the Interventional Procedures Advisory Committee in making recommendations about the safety and efficacy of this interventional procedure, which resulted in the "Interventional Procedure Guidance 266", published in June 2008.[71] The guidance does not cover whether or not the NHS should fund a procedure.

In the papers discussed (Table 3.1), a technical success was achieved in 75-88% of transluminal (i.e. transarterial or transvenous) procedures and in 93-100% of patients treated with the transapical approach. Hemodynamic improvement assessed by echocardiography was significant in all case series. In one case series of transluminal aortic valve replacement, all survivors improved by at least one NYHA class after the procedure and in another, half of the 43 patients who had successful procedures improved by at least one NYHA class.

A third case series of 21 patients (all in NYHA class IV at inception) who survived beyond 33 days reported that 5 patients improved to NYHA class I, 14 to class II and 2 to class III.

In three case series, longer term survival was 81% (35/43; median follow-up at 359 days)[32], 45% (5/11; median follow-up at 305 days)[69] and 41% (11/27; follow-up at 6 months)[35]. In case series of the transluminal approach, 30-day mortality ranged from 12-22% and from 10-14% in the transapical approach. Complications (within 30 days) from the transluminal approach were reported as follows: stroke in 2-12% of patients who underwent successful transluminal procedures, bradyarrhythmia in 36% (4/11), major bleeding in 18% (2/11), cardiac tamponade in 10% (9/86), iliac injury requiring major vascular repair in 5% (2/43) and access site infection requiring antibiotics in 5% (2/43). Complications from the transapical approach were reported as follows: pleural effusion in 31-37% of patients, two (3%) strokes, eight patients (14%) with transient hemofiltration, eight patients (14%) who required tracheostomy for weaning off ventilation, eight patients (14%) who required rethoracotomy, four patients (7%) requiring cardiopulmonary resuscitation, and three patients (4%) with pericardial effusion.

The ensuing guidance from NICE can be summarized as follows. The evidence on PAV implantation for AS is limited to small numbers of patients who were considered to be at high risk for conventional surgery. It shows good short-term efficacy but there is little evidence on long-term outcomes. There is a potential for serious complications, but the patients on whom this procedure has been used had a poor prognosis without treatment and were at high risk if treated by open heart surgery. Clinicians should ensure that patients understand the uncertainties about the procedure. PAV implantation is a technically challenging procedure that should be performed only by clinicians and interventional cardiology teams with special training. Units undertaking this procedure should have both cardiac and vascular surgical support for emergency treatment of complications. Details about all patients undergoing transcatheter aortic valve implantation for aortic stenosis should be entered into a central database.

#### *3.2.1.2 France: Haute Autorité de Santé*

This report has been published in January 2008. It took into consideration published literature (Table 3.1), unpublished data obtained from manufacturers (Edwards Lifesciences and CoreValve Inc) and expert opinion.[56] Results presented at oral presentations were not considered. In this HTA, evidence related to data obtained from 470 patients. 6-month survival of patients treated transluminally ranged in different series between 71 and 84%. Aortic valve opening and mean systolic transvalvular gradient improved from 0.6 $cm^2$ to 1.7 $cm^2$ and 45 mmHg to 10 mmHg respectively. In series reporting on the transapical approach, 6-month survival was 68%, aortic valve opening increased from 0.58 to 1.44 $cm^2$ and mean systolic transvalvular gradient improved from 46 to 9 mmHg.

The HAS recommends a conditional reimbursement of retrograde and transapical PAV insertion in patients that are considered at high risk of conventional surgery or deemed inoperable. The following prerequisites are formulated: reimbursement is limited in time, it is to be limited to specialised cardiac centres, all patients should be included in a mandatory registry. A re-assessment of reimbursement is intended to be completed when more data on clinical effectiveness have become available.

#### *3.2.1.3 Austria: Ludwig Bolzmann Institut*

In this HTA, literature is searched until Feb 2, 2008.[61] The articles included are enlisted in Table 3.1. The transapical approach is not taken into consideration in this report. All included studies were industry sponsored. They enrolled a limited number of patients and most authors reported only a short follow-up period (1 month). The case series reveal a favourable short term effectiveness of transluminal PAV: aortic opening increased from 0.49-0.72 $cm^2$ to 1-2 $cm^2$ and transvalvular systolic gradient decreased from 31-51 mmHg to 5.6-13.0 mmHg. Quality of life (QoL) measurements were not provided in any case series.

In some of them, NYHA class before and after the intervention was obtained and reportedly improved by one class after successful PAV insertion. One month mortality varied widely between case series, from 11 to 50% and was dependent on patient selection and operator experience. These mortality figures mostly were lower than those predicted by the EuroSCORE, although it is stressed that this risk tool mostly overestimates operative risk. Severe complications do occur such as stroke, myocardial infarction, severe bleeding, paravalvular leakage, vascular injuries, and cardiac tamponade.

It is concluded that current evidence does not allow a reliable assessment of the safety and the clinical effectiveness of the PAV technology because data originate from small patient series, and follow-up is too short.

### *Key points*

- **In 2008, three HTAs have been published on PAV. They all deplore that no randomised controlled trials are available enabling an assessment of the clinical effectiveness of PAV as compared to conservative or conventional surgical treatment.**
- **From case series in high-risk elderly patients, it is concluded that**
  **- PAV demonstrate good short-term efficacy but there is little evidence on long-term outcomes.**
  **- No data on the effects on quality of life are available.**
  **- The potential for serious complications and a high 6-month and 1-year mortality are noticed.**
- **One HTA recommends a provisional strictly regulated reimbursement of the technology. One HTA recommends no reimbursement because of lack of evidence. One HTA does not cover reimbursement issues.**

## 3.2.2 Case series of PAV insertion

So far, no randomised controlled trials that compared PAV with conservative medical treatment or with standard surgery have been published. Thus, for the time being, the assessment of the clinical effectiveness of PAV has to rely on published case series. Of 26 reports on PAV that we identified, 9 were "single case" reports. Because of their obvious anecdotal nature, these "single cases" will not be further discussed. Table 3.2 represents the 17 articles on the PAV that are considered in this review. Two papers that were not yet indexed by Medline when we performed our literature search, but became published in June 2008, were added to the list.[26, 60]

Case series reporting on Edwards PAV belong to one of three different types: the original antegrade approach where the PAV is delivered via the venous route ("the Rouen experience"), the retrograde approach by which it is delivered via an arterial route, and the transapical route requiring a mini-thoracotomy for delivery of the device via the apex of the left ventricle. Case series, reporting on the implantation of the CoreValve PAV, all have been using the retrograde approach.

**Table 3.2: Articles reporting case series on PAV implantation.**

| # | REFERENCE | TIME WINDOW | n |
|---|---|---|---|
| **Edwards, antegrade** | | | |
| 1 | Cribier A[14] | Apr 2002 - Aug 2003 | 6 |
| 2 | Cribier A[35] | Aug 2003 - NA | 36 |
| 2bis | Eltchaninoff H[31] | 2003 - 2005 | 36 |
| 3 | Sack S[63] | June 2005 - July 2005 | 2 |
| **Edwards, retrograde** | | | |
| 4 | Webb JG[64] | Jan 2005 - July 2005 | 18 |
| 4bis | Webb JG[32] | NA | 50 |
| 5 | Descoutures F[60] | Oct 2006 - Apr 2007 | 12 |
| **Edwards, apical** | | | |
| 6 | Lichtenstein S[65] | NA | 7 |
| 6bis | Ye J[66] | NA | 7 |
| 7 | Walther T[33] | Feb 2006 - Sep 2006 | 30 |
| 7bis | Walther T[26] | Feb 2006 - March 2007 | 50 |
| 8 | Walther T[67] | Feb 2006 - Oct 2006 | 59 |
| 9 | Svensson LG[34] | Dec 2006 - NA | 40 |
| **CoreValve, retrograde** | | | |
| 10 | Grube E[38] | Feb 2005 - Nov 2005 | 25 |
| 11 | Grube E[37] | Aug 2005 - Feb 2007 | 86 |
| 11bis | Marcheix B[68] | Dec 2005 - Aug 2006 | 10 |
| 11bis | Berry C[69] | March 2005 - Aug 2006 | 11 |

Edwards valves represent different generations of this PAV. Number followed by "bis" indicate follow-up studies incorporating the cohort discussed in preceding citation. In series 2 and 2bis, the retrograde approach was used in a minority of cases (see text). Time window: time period in which patient enrollment took place. NA: not mentioned in the paper.

### *3.2.2.1 Antegrade Edwards-PAV: the Rouen experience*

The first human PAV implant has been performed by Cribier in April 2002 and was reported in December 2002.[29] A second paper originating from Cribier's group reported on the acute and early follow-up results of the initial six patients treated with a PAV, all by using the antegrade approach.[14] All patients were in NYHA functional class IV. The PAV was successfully delivered in five patients. Early migration with subsequent death occurred in one patient who presented with a torn native valve, due to a preceding BAV. Acute hemodynamic and angiographic results showed no residual gradient, mild (three patients) or severe (two patients) paravalvular aortic regurgitation, and patent coronary arteries. On echocardiography, the aortic valve area was increased from 0.5 ± 0.1 cm² to 1.70 ± 0.03 cm². Marked and sustained hemodynamic and clinical improvement was observed after successful PAV implants. The first three patients died of a non-cardiac cause at 18, 4, and 2 weeks, respectively, and the other patients were alive at 8 weeks.

In August 2003, the Rouen investigators, in cooperation with the manufacturer, initiated a single-centre registry (in some papers erroneously denoted as "clinical trial") in order to study the feasibility and safety of compassionate PAV implantation in patients with end-stage aortic stenosis and no surgical options (the Initial Registry of EndoVascular Implantation of Valves in Europe [I-REVIVE] trial). 16 patients were enlisted in this registry but the data were not published separately. Most of these patients were treated via the antegrade approach. The retrograde approach was attempted in 7 patients but was not successful in three of them. With the acquisition of Percutaneous Valve Technology by Edwards Lifesciences, the registry protocol continued with some amendments (a.o. only the antegrade approach was used) from December 2004 on as the Registry of Endovascular Critical Aortic Stenosis Treatment (RECAST).[24]

The early and long term clinical results from 36 patients, enrolled in these registries, were reported in two separate papers, published in 2006 and 2007 respectively.[31, 35] The PAV that was used, was made of equine pericardium and labelled as "the Cribier-PVT valve" as previously described in this report. All patients were in NYHA class IV and had critical aortic stenosis (aortic valve area ≤0.7cm²) and severe comorbidities. Their mean age was 80±7 years (range 62-91). Twenty-seven patients were implanted successfully (23 antegrade, 4 retrograde). Eight patients underwent a BAV only, because PAV insertion was not successful. One patient died suddenly prior to the procedure and one patient died following pre-dilatation. Six patients had a complication during the procedure that led to death: 2 cardiac tamponade, 1 urosepsis, 1 complete heart block with failed resuscitation and 1 intractable hypotension. One patient developed a stroke during the procedure and died at day 33. One patient died within 30 days due to ventricular arrhythmia. Of 36 patients enrolled, 9 (25%) died because of conditions that could be attributable to the procedure and 8 of them died within 30 days (22%) (Table 3.3). For patients in whom PAV insertion was successful, there was an improvement in valve area (0.60 ± 0.11 cm² to 1.70 ± 0.10 cm²) and in transvalvular gradient (37±13 mm Hg to 9±2 mm Hg). Paravalvular aortic regurgitation was grade 0 to 1 (n = 10), grade 2 (n = 12), and grade 3 (n = 5). All patients experienced amelioration of symptoms. At six months, 22 of the initial population of 36 patients (61%) and 16 out of 27 (60%) successfully implanted patients had died. In about half of them, death was directly attributed to the intervention whereas the other deaths were related to the pre-existing comorbidities. The follow-up of patients later on has been reported in a subsequent paper.[31] One patient died at ten months (reason unknown) and one at 30 months (renal failure). Eventually, ten patients were followed-up at least for one year, 4 of them at least for 2 years and two of them for three years. In these survivors, PAV function remained stable.

Apart from the Rouen series, one German paper has been published, very briefly describing 2 patients in whom a PAV was successfully implanted via the antegrade approach.[63] In all other papers that we could retrieve on the subject, the retrograde technique was used.

#### *3.2.2.2 Retrograde Edwards-PAV*

For regulatory reasons (sic), the technologic ameliorations of the PAV that were implemented in 2004 after the acquisition of Percutaneous Valve Technologies by Edwards LifeSciences, could not be used in France before 2006 and were evaluated inititally by J. Webb in Vancouver, Canada.[36] Recently, a series of 12 patients originating from France has been published beyond the time window of our initial literature search, and has been added to this literature review (compare Table 3.1 with Table 3.2).[60]

Two case series in which the Cribier Edwards PAV was used, have been published by the Vancouver group.[32, 64] Their most recent paper reports on the initial 50 patients, treated with the equine epicardial trileaflet valve, inserted via the retrograde approach.[32] Presumably, the 18 patients reported in the first paper,[64] were part of the second series. Percutaneous transfemoral transarterial valve replacement was attempted in 50 high-risk symptomatic patients. High risk status was adjudicated by team consensus of cardiologists and cardiac surgeons when conventional surgery risk was considered excessively high in terms of anticipated mortality and morbidity. The predicted 30-day surgical mortality as assessed by the logistic EuroSCORE was 28. Mean age was 82±7 years (range, 62 to 94 years). Procedural success, defined as implantation of a functioning PAV within the aortic annulus and without in-laboratory mortality, was achieved in 43 patients (86%). Reasons for failure included inability to pass the iliac artery in 1 patient and to cross the aortic valve in 3 patients, a defective prototype delivery catheter in 1 patient, and malpositioning in 2 patients. One of these patients died during the procedure because of aortic injury. Transthoracic echocardiography documented an immediate reduction in transaortic mean gradient from 46±17 to 11±5 mmHg and an increase in estimated aortic valve area from 0.6±0.2 to 1.7±0.4 cm². Moderate paravalvular insufficiency was observed in 3 patients. Six patients (12%) died within 30 days consequential to ventricular arrhythmia, left main occlusion, iliac injury, stroke, and multiorgan failure. Three deaths occurred after 30 days as a result of respiratory failure, myocardial infarction, and renal failure, respectively (Table 3.3).

Before the procedure, 14% and 70% of successfully implanted patients (n=43) who reached the 1-month follow-up (n=37) were in NYHA functional class II and III, respectively, while 16% were in NYHA class IV. At 6 months, of 35 surviving and successfully treated patients, 17 were in NYHA class I, 17 in NYHA class II and 1 in class III. Of the 7 unsuccessful implants, one patient died during the procedure. Later on, 1 patient underwent a transapical PAV implantation (day 11) and 1 underwent conventional AVR at day 103. At a median follow-up of almost 1 year (359 days) 81% of patients that underwent successful PAV implantation remained alive. Echocardiography documented prosthetic valve durability with no structural or significant hemodynamic deterioration at a median follow-up of 359 days extending to a maximum follow-up of 734 days. Of the 7 failed PAV replacements, five patients (71%) were alive at 12 months.

The French series of 12 patients described by Descoutures et al. represents a subgroup from 66 consecutive patients referred for treatment of severe AS.[60] 27 of these patients underwent conventional AVR and 27 high-risk patients had a contraindication for PAV, mostly because of too small iliac arteries, precluding a transarterial approach. Twelve patients with a predicted operative risk of >20% underwent transarterial insertion of an Edwards-Sapien PAV. Their mean age was 85±6 years. Three (25%) were in NYHA class III and 9 (75%) in NYHA class IV. Correct insertion was obtained in 10 patients (83%). In one patient, a second PAV had to be inserted ("valve-in-valve") because of a severe intravalvular leak after placement of the first prosthesis. In 4 out of 10 successful implants, there was residual paravalvular regurgitation. In-hospital death was 25% (3 cases): one patient died during the procedure and two others at 24h and 4 days respectively (Table 3.3). There were no additional deaths after six months follow-up. At six months, 2 patients (22%) were in NYHA class I, 5 (56%) in NYHA class II and 2 (22%) in NYHA class III.

#### *3.2.2.3 Transapical Edwards-PAV*

The initial experience with the transapical approach for PAV implantation was also reported by the group from Vancouver.[65] A Cribier-Edwards equine pericardial valve was inserted in 7 patients, aged 77±9 years. They were severely symptomatic and considered at unacceptably high risk for surgery and not suitable for a transfemoral percutaneous PAV implantation due to aorto-iliac disease. Echocardiographic mean aortic valve area was 0.7±0.1 $cm^2$. All patients received 26-mm-diameter prostheses. Final positioning was judged optimal in 5 patients. Some degree of paravalvular insufficiency after initial deployment was evident in all patients. Postprocedural transthoracic echocardiography reported a median transaortic gradient of 9±6 mm Hg (interquartile range) and an aortic valve area of 1.8±0.8 $cm^2$ (interquartile range). One patient died at day 12 of pneumonia. Two other patients died at day 51 and 85 respectively while the other completed six-month follow-up, as reported in a separate article.[66]

A German single centre "proof of concept" series was published by Walther et al. from Leipzig, using the transapical technique for insertion of the Cribier-Edwards PAV as described earlier.[33] This series included thirty consecutive patients, treated between February and September 2006, aged 82±5 years. They had an estimated operative risk calculated according to EuroSCORE of 11.3±1.7%. All suffered severe symptomatic aortic stenosis (aortic valve area <0.9 $cm^2$). Valve implantation was performed using extracorporeal circulation (ECC) in 13 patients and without ECC support in 17 patients. Valve implantation was successful in 29 of 30 patients. Three patients (10%) died in-hospital. One required re-operation on postoperative day 37 due to new onset severe aortic valve regurgitation. Postoperatively, two patients required a permanent pacemaker because of complete heart block, requiring resuscitation in one. Aortic incompetence was diagnosed in 14 patients prior to discharge.

The same authors very recently published an update on this single centre series, covering 50 patients, treated between February 2006 to March 2007.[26] Although in their first report, the authors indicated they used the Cribier Edwards PAV, whereas in the "update" the Edwards Sapien was used, we presume that patients from the first series were included in the second because the time window started in both cases in February 2006 and in their second paper, the authors report on their "initial 50 patients".

Mean age of patients was 82.4±4.6 (range:65-93) years. Logistic EuroSCORE was 27.6±12.2. A "technically possible implantation" was reported in all patients although in their previous report, valve implantation reportedly was not successful in 1 of 30 patients. Moreover, in three patients early conversion to conventional sternotomy was needed because of valve dislocation or coronary problems that had been induced by the procedure. Based on this interpretation, we re-calculated an immediate success rate of 46/50 (92%). At 30 days postoperatively, four patients (8%) had died. Actuarial survival at 1 month, 6 months and 1 year was 92±3.8%; 73.9±6.2% and 71.4±6.5% respectively. At inception, patients were in NYHA functional class III or IV. No post-procedural data related to quality of life or functional class were provided.

A multicentre report, initiated by the Leipzig group and incorporating experience from Vienna, Frankfurt and Dallas, was reported shortly after publication of the first single centre experience.[67] It covers a time window from February 2006 to October 2006. Fifty-nine patients (81±6 years, 44 female) were operated at 4 centres. Average EuroSCORE was 11.2±1.8. Transapical PAV valve positioning was performed successfully in 55 patients (93%), and 4 required early conversion to sternotomy. Thirty-one patients were operated without the use of ECC. Post procedural echocardiography revealed paravalvular leakage in 26 patients (trace in 11, mild in 12, and severe in 3). Eight patients died in-hospital (13.6%). Actuarial survival was 75.7±5.9% at a follow-up interval of 110±77 days (range 1 to 255 days) (Table 3.3). The authors did not provide data on post-procedural functional status or quality of life.

Very recently, Svensson et al. reported on a Food and Drug Administration (FDA) approved feasibility study incorporating 40 patients treated between December 2006 and February 2008 with a transapical inserted Edwards equine or bovine PAV.[34] Patients were required to be at least 70 years, to present with severe aortic stenosis (valve area ≤0.6 cm²) and considered inoperable or at very high risk for surgery. Their EuroSCORE was 35.5±15.3% Mean age was 83.0±7.5 (range:69-93) years. A 33F sheath was used in the first 20 patients and 26F in de second 20. Ten patients required ECC because of intraoperative problems. Successful seating of the PAV was obtained in 35 patients, while in 5, open AVR was needed because of migration of the PAV or because of severe aortic regurgitation. There were 3 deaths at the day of operation. There were seven 30-day deaths (17.5%) and 9 (22.5%) in-hospital deaths (Table 3.3). From baseline to 30-day follow-up, mean effective aortic valve area increased from 0.62±0.12 to 1.61±0.37 cm². At 30 days, no perivalvular leakage was present in 19%, grade 1 in 46%, grade 2 in 31%, grade 3 in 4%, and grade 4 in none. One patient underwent delayed operative aortic valve replacement for perivalvular leakage. On follow-up after discharge from hospital, 6 additional patients died. The Kaplan-Meier curves showed 81.8% (1 month), 71.7% (3 months), and 58.7% (6 months) survival. Mean NYHA class at inception was 3.33; at 1 month it was 2.25, at 3 months 1.81 and at 6 months 2.08. Quality of life scores improved from preoperatively (SF-12 Physical 28.7, SD 6.1; Mental 48.1, SD 11.5) to postoperatively at 6 months (SF-12 Physical 35.2, SD 7.4; Mental 50.4, SD 11.7).

Interestingly, the authors also report the fate of patients that were referred to their respective institutions for potential PAV insertion, but who ultimately were not treated with a PAV. Of the 71 patients referred to Medical City Hospital, Dallas, 14.1% (n = 10) received a conventional surgically inserted valve (no peri-operative deaths) and 21% (n = 15) transapical or transfemoral PAV with 13.3% mortality. 46 patients (65%) were further treated medically. For the 92 patients referred to the Cleveland Clinic, 20% (n = 19) had conventional open surgery with no operative deaths, 19.6% (n = 18) underwent transapical or transfemoral PAV with 5% 30-day deaths, and 20% (n = 19) underwent balloon valvuloplasty with 4% mortality. 36 patients (39%) were further treated medically. The authors conclude that for patients referred for screening for PAV, open conventional surgery is preferable if deemed feasible by experienced surgeons, with no deaths in their series.

### *3.2.2.4 CoreValve PAV*

In the Siegburg First-in-Man study, a series of 25 patients is described in which first and second generation CoreValve PAVs were implanted.[38] It is a nonrandomised, single-centre registry to evaluate the feasibility and safety of implantation of the CoreValve PAV in high-risk patients with aortic valve stenosis, deemed inoperable because of concomitant comorbid conditions. Vascular access was obtained by standard surgical cut down of the common iliac artery in 9 patients, subclavian artery in 3 patients, and common femoral artery in 13 patients (second-generation device only). The procedure was performed with the patient under general anaesthesia. Extracorporeal circulatory support was activated just before device placement across the native valve position and terminated several minutes later immediately after withdrawal of the delivery catheter. Mean age of patients was 80.3 ±5.4 years. Eighty percent were females. All patients had severe symptomatic aortic valve stenosis with a peak trans-valvular aortic pressure gradient of 69.3±13.9 mm Hg (range, 34 to 139 mm Hg). The pre-procedural mean calculated aortic valve area was 0.72±0.13 $cm^2$. In 17 patients (68%), aortic regurgitation was also present. The median calculated logistic EuroSCORE of the study population was 11.0% (interquartile range, 9.2% to 19.9%), and 96% of patients were in NYHA functional class III or IV. Acute procedural success was achieved in 21 of 25 patients (84%). In 2 patients, emergency standard AVR had to be performed and 2 other patients died early after the procedure. Peak pressure gradient decreased to 21.31±5.05 mmHg after implantation. The degree of aortic regurgitation immediately after valve implantation was improved or unchanged in 16 patients (76.2%) and worsened in 5 patients (by 1 grade in 2 patients, by 2 grades in 3 patients). In-hospital mortality rate was 20% (5 of 25 patients). The valve was successfully implanted without peri-procedural events in 17 of 28 patients (68%).

The Siegburg experience was supplemented with that obtained in Leipzig (Germany) and Montreal (Canada) in a single paper that reports the results of second and third generation CoreValve implants in 86 patients.[37]

Clinical inclusion criteria were the following: severe native aortic valve stenosis with an area <1 $cm^2$ or <0.6 $cm^2/m^2$ with or without aortic valve regurgitation and age ≥80 years, or a logistic EuroSCORE of ≥20% for the 21F group and age ≥75 years, or logistic EuroSCORE ≥15% for the 18F group, respectively, or age ≥65 years and at least one of a series of severe comorbid conditions. The mean age of patients was 82.2±5.9 years. 65% were females. Overall logistic EuroSCORE was 21.7±12.6. Adequate device insertion was obtained in 76 of 86 enrolled patients (88%). Five deaths occurred periprocedurally and overall mortality at 30 days was 12% (Table 3.3). Successful PAV insertion resulted in clinical and hemodynamic improvement. The mean NYHA class declined from 2.85±0.73 before the procedure to 1.85±0.60 afterwards. In 51 (66%) patients, the aortic regurgitation grade remained unchanged or was even reduced after the procedure. On the contrary, a worsening of the preinterventional aortic regurgitation grade after the procedure was noted in 26 patients. All of them were related to paravalvular leakages as determined by echocardiography. Severe postprocedural aortic regurgitation was not present in any patient. Major adverse events were stroke in 10% (9/86) of patients and cardiac tamponade in 9% (8/86). The combination of death, stroke or MI occurred in 17% (14/86) of patients. In terms of acute device success and safety, no differences were noticed between the second (n=50) and third (n=36) generation devices. The major advantage of the smaller 18F sheath was found to be in a lower need for surgical cut-down of the vascular access site and consequently more procedures being performed only with local anaesthesia of the groin.

Two separate articles have been published by the Montreal group report on 10[68] and 11[69] patients respectively, treated with the second generation Corevalve PAV. At least part of these patients presumably is included in the multicentre register described above, given the reported time window of patient enrollment in the different articles. Femoro-femoral ECC was provided in all patients. Of 11 patients successfully treated with the PAV, one had a peri-procedural stroke and died 5 days post intervention. Four other patients died within 4 months of hospital discharge. The median duration of survival of the survivors was 305 (range 249–431) days.

### *Key points (cf. Table 3.3)*

- **There is no data on the performance of PAV insertion based on randomised controlled trials.**
- **Published case series indicate that PAV insertion is feasible in the hands of experienced operators in up to 90% of elderly patients with symptomatic AS, deemed inoperable or at unacceptable high risk for surgery.**
- **PAV insertion in these populations is a risky intervention with a procedure attributable mortality rate of 12% in the largest transarterial PAV insertion and 8-22.5% in transapical series from experienced centres. In these patients, it is uncertain what their mortality would have been if they had been operated conventionally or treated medically.**
- **Vascular complications occur especially when the transfemoral route is used, with an incidence of 10-15%. Stroke has been especially observed in the transfemoral approach, and occurs in 3-10% of cases.**
- **The short term efficacy of PAV seems to be good. Patients in whom a PAV has been successfully inserted are reported to experience an improvement in their NYHA functional class (from NYHA III → NYHA I/II), in accordance with an improved valvular function by echocardiography and doppler.**
- **It is not clear what the real impact of PAV would be on a generic measurement of QoL.**
- **There is no data on the long term clinical effectiveness of PAV insertion as compared to medical therapy or conventional surgery.**

**Table 3.3: Feasibility, safety and survival data extracted from published case series of PAV.**

| Ref | PAV type and approach | n | age | immediate success | procedure attributable mortality* | 30 day survival* | 6 month survival | | | Logistic Euro SCORE |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | all | all | success | failed | |
| Cribier | Edw. Antegr. | 36 | 80±7 (range 62-91) | 27 (75%) | 9/36 (25%) | 28/36 (78%) | 14/36 (39%) | 11/27 (41%) | 3/9 (33%) | NA |
| Webb | Edw. TF | 50 | 82±7 (range 62-94) | 43 (86%) | 6/50 (12%) | 44/50 (88%) | 41/50 (82%) | 35/43 (81%) | 6/7 (86%) | 28 |
| Descoutures | Edw. TF | 12 | 85±6 | 10/12 (83%) | 3/12 (25%) | 9/12 (75%) | 9/12 (75%) | NA | NA | 31,1±14,4 |
| Walther multicentre | Edw. TA | 59 | 81,4±5,8 | 55/59 (93%) | 8/59 (13,6%) | 51/59 (86%) | NA | NA | NA | 26,8±13,5 |
| Walther single centre | Edw. TA | 50 | 82,4±5 | 46/50 (92%) | 4/50 (8%) | 46/50 (92%) | KM 73,9% | NA | NA | 27,6±12,2 |
| Svensson | Edw. TA | 40 | 83,0±75,2 (range 69-93) | 35/40 (87,5%) | 9/40 (22,5%) | 33/40 (82,5%) | KM 58,7% | NA | NA | 35,5±15,3 |
| Grube | Core Valve TA | 86 | 82,2±5,9 | 76/86 (88%) | 10/86 (12%) | 76/86 (88%) | NA | NA | NA | 21,7±12,6 |

References: see Table 3.2 and text. *Procedure related mortality mostly equals 30-day mortality, except in cases where it was explicitly reported that a procedural complication led to death beyond 30 days. "success"=patients in whom PAV implant was successful. "failed"=patients in whom PAV implant failed. n=number of patients in the case series. KM=Kaplan-Meier estimate. TA=transapical. TF=transfemoral. NA=not available.

## 3.3 LITERATURE REVIEW – PERCUTANEOUS PULMONARY VALVE

A search for HTA reports on PPV by consulting the database of CRD did not lead to any result. Hand-searching led to two HTA reports. Our search for primary literature resulted in 12 eligible articles related to PPV (Figure 3.1).

### 3.3.1 Health technology assessments

Two reports are discussed in this paragraph: one HTA originating from NICE ("Interventional procedure overview")[58] and one systematic review from Austria, published in March 2008.[59]

#### *3.3.1.1 U.K.: NICE*

This report on PPV from NICE is not a formal HTA, but an "Interventional Procedure Overview" that was prepared in February 2007. It is based on a rapid review of the medical literature (search until March 15, 2007) that led to the inclusion of two case series and two case reports. Furthermore, specialist advisers' opinions were asked for.[58] This report has been prepared to assist members of the Interventional Procedures Advisory Committee in making recommendations about the safety and efficacy of the interventional procedure, which resulted in the "Interventional Procedure Guidance 237", published in November 2007.[72] The guidance does not cover whether or not the NHS should fund a procedure.

Across the case series and case reports, PPV insertion was successful in 98-100% of patients. One case series of 59 patients reported a significant decrease in the mean systolic pressure gradient across the RVOT from 33.0 mmHg before to 19.5 mmHg after the procedure. In this series, median NYHA class improved from class II at baseline to class I at 10 months. In one series (n=59), severe bleeding and right hemothorax was reported in one patients (2%) and minor dissection of an existing homograft was reported in another. There was no mortality. It was concluded that the evidence on PPV implantation for RVOT dysfunction is limited to small numbers of patients but shows good short-term efficacy, that there is little evidence on long-term efficacy and that there are no particular safety concerns in the context of a condition that otherwise requires open cardiac surgery. It is stated that clinicians should ensure that patients understand the uncertainties about the procedure and that there will be a need for repeat procedures or operations. PPV implantation is a technically challenging procedure that should be performed only by clinicians and teams with special training and experience in interventional congenital cardiology. Units undertaking this procedure should have both cardiac and vascular surgical support for emergency treatment of complications. Details about all patients undergoing PPV implantation for RVOT dysfunction should be entered into a central database.

#### *3.3.1.2 Austria: Ludwig Bolzmann Institut*

Literature search for this HTA was performed until February 2008. This report summarizes data from 6 case series and 2 case reports. After insertion of a PPV, regurgitation fraction decreased by 62-90%, and pressure gradient across the RVOT by 36-52%. Median functional class improved from NYHA II to NYHA I. There was no procedure related mortality. Postoperative complications were severe bleeding (1/59, 2%) and conversion to conventional surgery in 3/76 patients (4%). During follow-up (maximum 33 months) related to 123 patients, 10 cases of in-stent restenose, 26 cases of stent fracture and 1 case of stent migration were reported. The authors of this HTA report concluded that no randomised trials were available and that mean follow-up extended to no more than 16 months. Available data suggested a benefit of the procedure and a restricted reimbursement was recommended in specialized centres with a mandatory registration of all cases and a re-evaluation later on.

### *Key points*

- **HTAs stress that no randomised controlled trials are available enabling an assessment of the clinical effectiveness of PPV as compared to conventional surgical treatment.**
- **From case series, it is concluded that PPV demonstrate good short-term efficacy (mean follow-up <2 years) but there is little evidence on long-term outcomes.**
- **There are no particular safety concerns in the context of a condition that otherwise requires open heart surgery.**
- **One HTA recommends a restricted reimbursement of the technology. One HTA does not cover reimbursement issues.**

## 3.3.2 Case series

Our search for primary literature resulted in 12 articles related to PPV insertion: 4 were single case reports, 1 article reported on three cases, and the remaining 7 papers all originated from a single operator, i.e. Philipp Bonhoeffer, who treated his first patients in Paris (France: Hôpital Necker Enfants Malades) and later on in three different centres in London (UK: Great Ormond Street Hospital for Children, The Heart Hospital, and The Harley Street Clinic). The most recent paper from his group reports data on 155 patients and was published in Circulation in April 2008.[40] This paper is discussed here in more detail.

The authors collected 163 patients that from a clinical point of view were considered suitable candidates for the intervention. Inclusion criteria were based on surgical indications for RVOT revision (severe right ventricular hypertension, pulmonary regurgitation with severe right ventricular dilatation, impaired exercise capacity). Exclusion criteria were pregnancy, occluded central veins, active infection or weight less than 20 kg. Morphological suitability for PPV was assessed by measuring the RVOT using magnetic resonance imaging or angiography and by balloon sizing in some patients with borderline anatomy. Angiography of the ascending aorta was performed to assess coronary arteries morphology, sometimes leading to coronary angiography. Based on these morphologic data, 8 of 163 patients were excluded from the PPV procedure, because of unfavorable RVOT dimensions or risk of coronary artery compression.

Between September 2000 and February 2007, 155 patients underwent PPV implantation. The median age of the patient population was 21.2 years (range 7 to 71 years); 57 patients were <16 years old (37%), and 42% were female. Most patients (61%) had tetralogy of Fallot or a variant morphology. 92% of patients had a conduit from the right ventricle to the pulmonary artery placed at previous surgery, most of them valved with a homograft. The PPV insertion procedure was successful in 150 cases (97%), indicating that the PPV was successfully seated within the RVOT. Complications occurred in 12 patients (7.7%), 7 of which were considered as major. In 5 of these patients (representing the "failed" procedures), the PPV had to be explanted surgically because of valve dislodgement, homograft rupture, coronary artery obstruction or pulmonary artery obstruction. One other patient required surgery for bleeding after homograft rupture and one patient was resuscitated after homograft rupture but recovered. Two patients in whom the procedure was undertaken because of cardiogenic shock, died early. There were no other deaths, resulting in an overall early mortality of 2 patients (1.3%). The incidence of procedural complications fell from 6% in the first cohort of 50 cases to 2.9% in the second cohort of 105 patients. During later follow-up, two patients died suddenly at 8 and 35 months. At autopsy, the aspect of the PPV was normal. Overall, four of 155 patients died (2.6%) during a median follow-up of 28.4 months. Follow-up ranged from 0 to 83.7 months. Echocardiography showed a significant reduction in right ventricular systolic pressure (from 63±18 to 45±13 mm Hg) and right ventricular outflow tract gradient (from 37±20 to 17±10 mm Hg). Valvular competence was well maintained during follow-up (median 28.4 months). Valve regurgitation was absent or trivial in 80% of cases at 36 months (n=32). Moderate regurgitation was only seen in 2 patients in the context of endocarditis.

Redo-procedures were needed in a substantial part of the cohort and consisted either of transcatheter reinterventions or surgical revision (reoperations). Freedom from reoperation was 93±2% and 86±3% at 10 and 30 months, respectively. Surgical explantation and replacement of the valve was needed in 23 patients. In 5 of them, this occurred in the acute phase (cf. 5 "failed procedures" in the initial cohort) whereas in 18 others, it occurred later (2 to 70 months). Late reoperation was needed because of "outgrown conduit" in 3 patients, "hammock effect", stent fracture, endocarditis or residual stenosis. The "hammock effect" refers to an observation that a valve did not appose to the stent and was due to the design of the first generation device. In four patients it led to reoperation whereas in 7 patients it could be corrected by catheter reintervention. The "hammock" design flaw has been corrected since its recognition.[39] Furthermore, a learning curve was noted as far as the need for explantation of the PPV was concerned: of the first 50 patients, 16 underwent device explantation compared with 5 patients in the second cohort of 105 patients. In an interim analysis of patients treated until September 2004, if only the second generation valve design was taken into consideration, freedom from reoperation at 24 months was 91.7%.[73]

Freedom from transcatheter reintervention was 95±2% and 87±3% at 10 and 30 months respectively. A transcatheter reintervention with implantation of a second valve ("stent-in-stent") was performed in 19 patients, whereas in 3 patients the reintervention was limited to balloon dilatation of the device. Transcatheter reinterventions were predominantly due to stent fractures. In 17 out of 26 cases (i.e. 21.1% of a series of 123 patients treated with PPV) described previously by Nordmeyer, fracture did not lead to loss of stent integrity during a follow-up of 0-843 days.[20] Stent fracture–free survival at 1 year was 85.1%; at 2 years, 74.5%; and at 3 years, 69.2%. In this interim analysis, replacement of the valve was needed in 9 (35%) patients in whom stent fracture was recognized. Freedom from transcatheter reintervention did not differ significantly in the 2 chronological cohorts (n=13 versus n=9) due to the fact that reinterventions were performed predominantly due to stent fractures, a complication that was not affected by the learning curve.

Within the second cohort of 105 patients (exact follow-up time unclear from paper, range: 0-40 months), 13% of them (14/105) needed a repeat intervention, in 9 of the cases (8.5%) a transcatheter valve-in-valve insertion and in 5 cases (4.5%) a new surgical valve implantation.

Long-term patient survival data were not unequivocally reported. Although a survival at 83 months reportedly was 96.9%, it can be inferred from figure 4A in the paper (data on freedom from re-operation) that only 2 of 155 patients were followed for 82 months. It is mentioned that 4/155 patients died during follow-up. Two of them who presented in cardiogenic shock at the time of the procedure died 24 hours and six weeks respectively, after the procedure. Two other patients died suddenly at 8 and 35 months respectively. As estimated from figure 4A, 39 patients were followed for at least 40 months.

**Table 3.4: Summary of feasibility and safety data from Bonhoeffer's series on PPV.[40]**

| Ref | PPV type | n | meadian age (range) | immediate succes | procedure related mortality | 30 day survival | Survival |
|---|---|---|---|---|---|---|---|
| Lurz | Melody | 155 | 21,2 (7-71) | 150 (97%) | 2/155 (1,3%) | 154/155 (99,4%) | Median follow-up 28 mo: 4 deaths. |

### *Key points*

- **There is no data on the performance of PPV insertion based on randomised controlled trials.**
- **The feasibility of PPV insertion is well documented in the hands of one single operator: in almost all selected patients PPV insertion was feasible.**
- **The mortality risk of PPV insertion is very low.**
- **The short term (median follow-up 28 months) efficacy of PPV is good. Patients in whom a PPV has been successfully inserted have an improved valvular function by echocardiography and doppler. In a recent cohort of 105 patients, a redo-valve implantation was needed in 13% of cases, within a follow-up period of 0-40 months.**
- **There are no data on the longevity of PPVs.**
- **There is no information on QoL measured with a generic instrument.**
- **The optimal timing of the procedure in order to prevent right ventricular failure and late ventricular arrhythmias is unknown. The long-term effectiveness as compared with (delayed) surgery is unknown.**

# 4 PATIENT ISSUES

## 4.1 PERCUTANEOUS AORTIC VALVE

PAV largely remains an investigational procedure with a substantial early risk of death and an unknown long-term effectiveness. It has not yet been clarified if the mortality risk associated with the percutaneous procedure is lower than that incurred by conventional surgery. Before submitting patients to PAV insertion, they should be clearly informed about the uncertainties surrounding the intervention. This may require an intense effort from the part of the physician but should not be overlooked, given the vital importance of whatever decision. The position of PAV within the management spectrum of patients with aortic stenosis is not well defined. As argued by Chantler, after establishing a diagnosis (in this case: "diagnosis of severe symptomatic aortic stenosis"), the task for a doctor is to discuss what can be done and what should be done; the two are not synonymous.[74] The question to be answered is to what extent the patient's quality of life will be improved, provided he/she survives the intervention. There are no sound criteria to assess the appropriateness to proceed to correction of the valvular dysfunction (whether by surgery or PAV) in a frail elderly patient with symptomatic aortic stenosis and substantial co-morbidities, or rather to opt for a conservative treatment. Depending on the pre-procedural clinical condition, the quality of life may hardly be altered by a successful PAV insertion. In this respect, the 2006 AHA/ACC (American Heart Association / American College of Cardiology) guidelines on the management of patients with valvular heart disease mention the following related to elderly patients:[6] "Valve replacement is technically possible at any age, but the decision to proceed with such surgery depends on many factors, including the patient's wishes and expectations. … Certainly advanced cancer and permanent neurological defects as a result of stroke or dementia make cardiac surgery inappropriate. Deconditioned and debilitated patients often do not return to an active existence, and the presence of the other comorbid disorders could have a major impact on outcome." This statement contrasts with co-morbid conditions that are reported in some of the patients enrolled in published PAV case series including stroke, dementia, and malignancy. In a series of 7 patients, two were treated with PAV and were not accepted for conventional AVR because of "multiple stroke with dementia" in one and "end stage lung disease" in a second.[66] The appropriateness of PAV insertion in another published case is also questionable: "His past medical history included coronary artery disease (CABG in 1972 and 1980, transmyocardial laser revascularization in 1998, multiple percutaneous coronary interventions), left ventricular dysfunction (ejection fraction 20%), ventricular tachycardia (implantable cardiovertor defibrillator), left nephrectomy for renal cell carcinoma, end-stage renal disease on hemodialysis,…"[75] One may wonder if "care" may not be a better option than "cure" in this kind of patients.

The same reasoning is promulgated by Fisken: "We hear a lot about the right of people to die with dignity. Such discussions usually occur in the context of malignant disease or other major progressive illnesses such as motor neurone disease. It is surely worth highlighting the problem of undignified death in those who simply have multiple pathologies related to ageing and whose quality of life has deteriorated to a point where they seem to have little, if any, enjoyment left in carrying on."[76]

### *Key point*

- **Before submitting patients to PAV insertion, they should be well informed about the prevailing uncertainties surrounding the benefit they can expect from PAV insertion as compared to a conservative therapy or surgical AVR.**

## 4.2 PERCUTANEOUS PULMONARY VALVE

Safety is a less problematic issue in PHV insertion in patients with degenerated RVOT disease. PPV is a reasonable option for patients that otherwise should undergo open heart surgery although the optimal timing of the intervention is unknown. Patients should be informed about these uncertainties and about the risk for the need of a redo-intervention.

### *Key point*

- **Patients undergoing PPV insertion should be informed about the uncertainties surrounding the optimal timing of the procedure and the potential for redo-interventions because of early device failure.**

# 5 COST CONSIDERATIONS

In this part Belgian cost data on percutaneous heart valve implantation were searched. Next, we tried to identify economic evaluations in the international published literature. Finally, since relatively few data are available, some general thoughts on gathering data (in time) are given.

## 5.1 COST INFORMATION

Different sources were consulted to gather cost information on percutaneous aortic or pulmonary valve implantation. The website of the NIHDI (National Institute for Health and Disability Insurance) and the Technical Cel (TCT, Technische Cel / Cellule Technique) were searched. Finally, because no detailed information on these new interventions could be identified, a short-term cost analysis was performed for percutaneous pulmonary valve implantation.

### 5.1.1 NIHDI

The reimbursement fees for procedures related to (pulmonary or aortic) valve replacement were searched on the NIHDI website. An overview of identified nomenclature numbers and a description is given in Table 5.1.

**Table 5.1: Charges with respect to heart valve interventions**

| Nomenclature number[a] | Description | Honorarium[b] |
|---|---|---|
| 229014 - 229025 | Operatie op het hart of op de grote intrathoracale bloedvaten, met extracorporale circulatie | 2163.04 € |
| 229515 - 229526 | Operatie op het hart of op de grote intrathoracale bloedvaten die het plaatsen omvat van meer dan een kunstklep of van een valvulair homogreffe of van één kunstklep en een myocard-revascularisatie, met extra-corporele circulatie | 3090.05 € |
| 229596 - 229600 | Operatie op het hart of op de grote intrathoracale bloedvaten die de plastiek of het plaatsen van een kunstklep omvat, met extracorporele circulatie | 2403.37 € |
| 269290 - 269301 | Weefsels van menselijke oorsprong, hartklep van menselijke oorsprong, in België afgeleverd, verzendingskosten inbegrepen | 2666.19 €[c] |
| 589190 - 589201 | Percutane endovasculaire plastiek van de aortaklep, van een aangeboren misvorming van de aorta, van de pulmonalisklep, de mitralisklep, de tricuspidklep of fulguratie van een klep inclusief de manipulaties en controles tijdens de behandeling en de gebruikte catheters, exclusief de dilatatiecatheter(s) en farmaca en de kontrastmiddelen, maximum per operatiezitting | 1555.43 € |
| 684736 - 684740 | Hartklep | Tariffs for this code number are published in lists (see Table 5.2). |

Source: Nomensoft (https://www.riziv.fgov.be/webapp/nomen/Search.aspx?lg=N, accessed August 21, 2008)
a: The first and second number are for ambulatory and hospitalised patients, respectively; b: Prices in 2008. There is a full reimbursement for both preferential and non-preferential insured patients; c: Average price in 2007, based on source: Doc N RIZIV (No hororarium or reimbursements are mentioned in Nomensoft for this number). The honorarium with this nomenclature number found in our database (see further) was €2553.30 (in 40 out of 47 cases). In four cases, this was €3400.

For heart valves, tariffs are published in specific lists, which are communicated in circular letters. Depending on the type of valve, different tariffs are charged. Table 5.2 gives a brief overview of these cost details for different type of heart valves. For each category, the minimum and maximum tariffs are presented.

**Table 5.2: Tariffs of heart valves**

| | A | B | C | D | E | F |
|---|---|---|---|---|---|---|
| Biological valves: porcine valves | | | | | | |
| Minimum* | 2703.87 | 2703.87 | 0.00 | 2027.91 | 675.96 | 148.74 |
| Maximum* | 2856.01 | 2856.01 | 0.00 | 2142.01 | 714.00 | 148.74 |
| Biological valves: pericardial tissue valves | | | | | | |
| minimum | 2706.50 | 2706.50 | 0.00 | 2029.88 | 676.62 | 148.74 |
| maximum | 3121.05 | 3121.05 | 0.00 | 2340.79 | 780.26 | 148.74 |
| Biological valves: stentless | | | | | | |
| minimum | 2703.87 | 2703.87 | 0.00 | 2027.91 | 675.96 | 148.74 |
| maximum | 3136.55 | 3136.55 | 0.00 | 2352.42 | 784.13 | 148.74 |

* This should not be interpreted as minimum and maximum prices as such. This are the lowest and highest prices ascribed to a certain valve within each category Source: http://www.riziv.fgov.be/care/nl/other/implants/general-information/circulars/2008/pdf/200804annexe1part2.pdf (accessed on August 21, 2008)
A: price (inclusive taxes on added value (TAV)); B: reimbursement for a non-preferential insured patient with a conventioned health care provider[xi] or reimbursement for a preferential insured patient; C: supplement for a non-preferential insured patient with a conventioned health care provider or supplement for a preferential reimbursed patient; D: reimbursement for a non-preferential insured patient with a non-conventioned health care provider; E: supplement for a non-preferential insured patient with a non-conventioned health care provider; F: delivery margin.

The price for percutaneous implantable heart valves was not included in these lists since they are not reimbursed. The price, however, is already determined at the Ministry of Economics. The Minister of Economics approved a retail price of €19 243.62 (excl. TAV) or €20 398.23 (incl. TAV) for both the Melody and Edwards SAPIEN heart valves and a retail price of €18 500 (excl. TAV) or €19 610 (incl. TAV) for the Corevalve Revalving™ system. The Melody valve was the first one to get its price assigned by a Ministerial Order of 2 February 2007. The justification mentioned this price was based on the European average minus a reduction taking into account that the Melody was only recently commercialized in several countries and thus the European prices were no real retail prices. This argument may be questioned since it is not clear why such a relative high price was set in other countries. Probably it is more a question of what the market is willing to pay instead of real underlying costs. The Ministerial Order of 15 May 2008 granted the same price to the Edwards SAPIEN valve justifying that this price is based on the price of the Melody. Again, this justification may be questioned. The price of the Corevalve was granted by the Ministerial Order of September 15, 2008. A discussion on a European level may be desirable to set a transparent and justified price.

### 5.1.2 TCT

The task of the Technical Cel (TCT, Technische Cel / Cellule Technique) is to link hospital data, validate them, and make them anonymous. It is based on linking the validated MCD (Minimal Clinical Data set) data of the Ministry with the invoice data of the INAMI/RIZIV, which come from the insurance institutes. This feedback only describes the "classic" hospitalisation, and not one-day clinic. Furthermore, it only includes costs reimbursed by the compulsory health insurance. Co-payments, excess fees, or reimbursement by other health insurance are not incorporated in these data. Data are available on APR-DRG (All Patient Refined Diagnosis Related Groups) level, which is further subdivided in four categories indicating the degree of severity.[xii] The linking percentage between the two databases improved from 80% in 1997 to 92% in 2000 and almost 96% in 2005.There are three APR-DRGs referring to valve disorders or interventions (Table 5.3).

[xi] Tariffs are arranged between representatives of health care providers, sickness funds and the government in commissions and meetings at the NIHDI. Every individual health care provider can accept the arrangements (convention) or not. In case of acceptance, the health care provider is "conventioned" and uses the official tariffs.

[xii] https://tct.fgov.be/etct/html/nl/fbho_faq.jsp

However, no separated category exists for aortic or pulmonary valve replacement and thus no specific information for these interventions is available. Therefore, details on these APR-DRGs are not further discussed.

**Table 5.3: APR-DRGs related to valve disorders or interventions**

| | |
|---|---|
| APR-DRG=162 | Interventions on heart valves, with heart catheterisation (ingrepen op hartkleppen, met hartcatheterisatie) |
| APR-DRG=163 | Interventions on heart valves, without heart catheterisation (ingrepen op hartkleppen, zonder hartcatheterisatie) |
| APR-DRG=200 | Congenitale heart and valvedisorders (congenitale hart en klepaandoeningen) |

## 5.1.3 An early short-term cost analysis for PPV replacement

Information on the cost of percutaneous heart valve devices is unavailable. No detailed cost analysis associated with this procedure was identified. Some authors forecast that a dramatic change is to be expected for the next decade, as the emergence of transcatheter repair techniques significantly reduce the risk and cost associated with surgical procedures.[77] No evidence of this could be identified. We have tried to estimate short-term costs for PPV insertion as compared to the standard operation which involves open heart surgery. The first PPV implant in Belgium was performed in the University Hospital Gasthuisberg (Leuven, Belgium) on November 28, 2006. It was performed by Prof. M. Gewillig assisted by Prof. P. Bonhoeffer, the inventor of this procedure. Until today, Prof. M. Gewillig and his team are the only persons who have performed this procedure in Belgium. We contacted Prof. M. Gewillig to help us gathering cost information for the PPV implantation and the implantation of a homograft by performing open heart surgery.

The lack of clear data on the current use of PAV in Belgium, which apparently occurs in a few centres across the country, prevented us to perform a comparable exercise for aortic stenosis treatment.

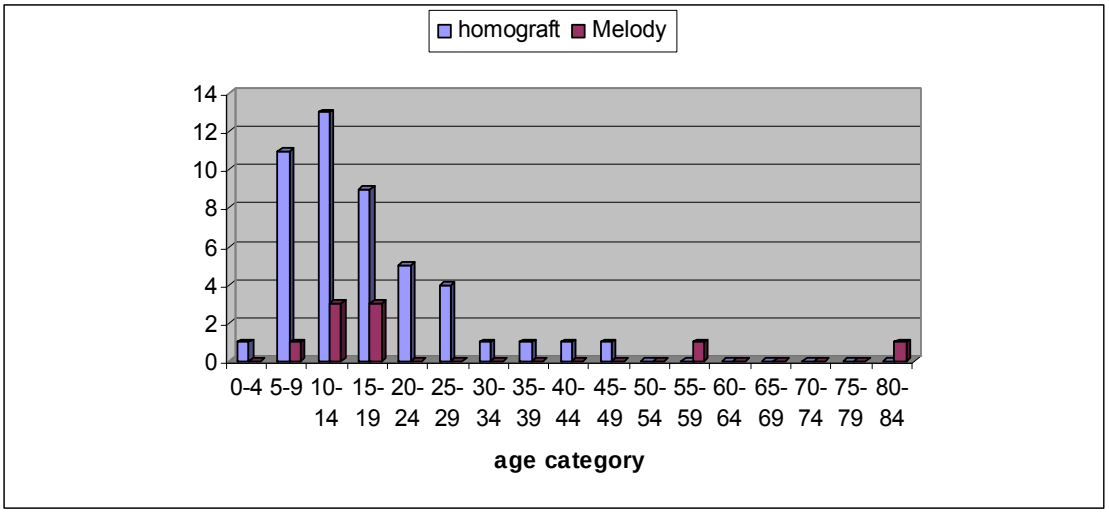
### *5.1.3.1 Population characteristics*

With respect to homograft implantation, only files after 2000 could be included since older files were not included in the hospital's administrative database. Thereby, only 47 homograft implantation files were received. For PPV implantation, there were 9 cases. Population characteristics were gathered item per item and not individual per individual to guarantee anonymity. Furthermore, they were collected separately from the cost data so identification of patients was not possible.

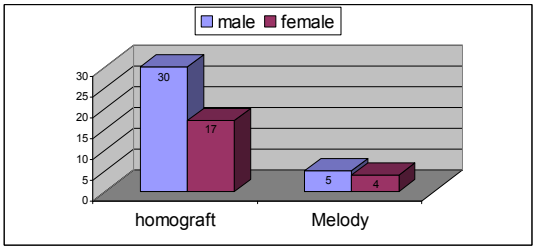
The population characteristics gathered were: age, gender, number of preceding sternotomies, and diagnosis (Figure 5.1). The mean age was 16.9 (range 4.5 – 48.4) and 25.8 (range 7.1 – 81.6) years in the homograft and Melody group, resp.. Two outliers of 57.7 and 81.6 years were observed in the latter. 63.83% and 55.56% was male in both populations, resp.. In the homograft group, 8.51%, 68.09%, 17.02%, and 6.38% had, resp. 1, 2, 3, or 4 preceding sternotomies. This was 44.44%, 33.33%, 22.22%, and 0%, resp., in the Melody group. The diagnosis was ToF and pulmonary stenosis (PS) in 72.34% (34/47) and 14.89% (7/47) of cases, resp. in the homograft group. This was 44.44% (4/9) and 33.33% (3/9), resp., in the Melody group.

**Figure 5.1: Population characteristics**

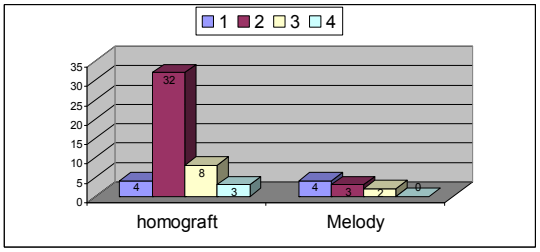
**Age**



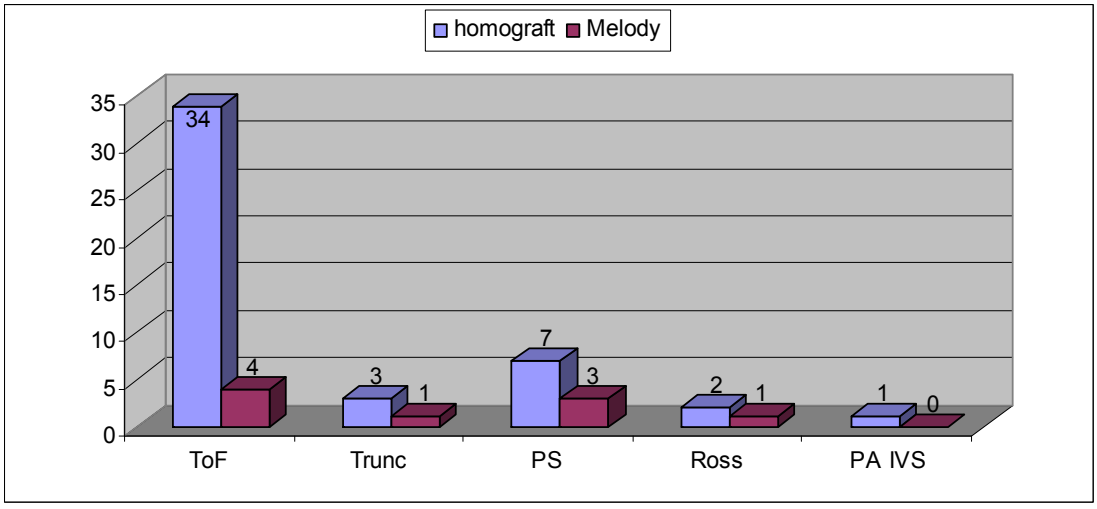

**Sex**




**Number of preceding sternotomies**




**Diagnosis**




PA IVS: pulmonary atresia with intact ventricular septum; PS: pulmonary stenosis; Ross: Ross operation; ToF: Tetralogy of Fallot; Trunc: truncus arteriosus.

### *5.1.3.2 Cost data*

Our calculations are limited to costs recorded in the hospital's database. Costs incurred outside the hospital or costs related to interventions in other hospitals are not included. Furthermore, only costs between 30 days before and 180 days after the index procedure, i.e. the day of the intervention, were included. The follow up of 180 days was complete for all files. No exact time of hospitalisation was mentioned to guarantee that patients could not be identified. The day of intervention was indicated as 'x' in all files. Other days were reported as the number of days before or after the index procedure. This masking happened at the hospital before files were transferred.

The mean cost of the device is clearly much higher for the Melody implantation in comparison to the homograft. The supplement for the former was €26 610.43 in all nine cases. This price includes in the first place the cost for the Melody valve of €26 461.69 and a delivery margin for the hospital pharmacist of €148.74 (i.e. 10% of the price of the product with a maximum of €148.74).

The price of the device was about €6 000 higher than the official price of €20 398.23, because at that time, there was no official price yet for this valve and a price of €26 461.69 was initially suggested by the manufacturer to the Ministry of Economics (demand of November 6, 2006). We adjusted our calculations for this difference since the official price was set at €20 398.23. In contrast, the average cost of the homograft device was €2672.30. In 40 out of the 47 cases, the cost was €2553.30. The minimum cost of the implant was €901.29, the maximum was €6054.15. However, the latter was a case in which two heart valves were charged. Excluding this unique case, the maximum was €3400.

Whereas the cost of the device is much higher for PPV implantation, the length of hospitalisation is much shorter, i.e. a mean duration of less than 4 days with PPV implantation. In contrast, with a classic homograft implantation this was almost 10 days. This, however, does not offset the higher cost of the implant in the short-term. The total costs for the NIHDI and patient co-payments, inclusive the device cost are about €27 750 with PPV implantation (Table 5.4) versus about €12 200 with a homograft (Table 5.5), a difference of more than €15 500. Of course, as mentioned before, this includes only the costs incurred in the short term in the selected hospital. More details can be found in the following two tables. Costs were disaggregated in the following categories: NIHDI payment, co-payment, supplement, insurance, and private payment. These costs were aggregated according to whether or not they occurred at the day of the intervention, before the intervention, or after the intervention. For the latter two categories a distinction was also made between costs during or outside the initial hospitalisation. Costs for supplements (exclusive the device), insurance and private payments were aggregated since these costs were very small or non-existing.

**Table 5.4: Length of hospitalisation and cost information for PPV in a university hospital in Belgium**

| | mean | st.dev. | minimum | maximum |
|---|---|---|---|---|
| **General information** | | | | |
| length of hospitalisation (days) | **3.67** | **1.66** | **3** | **8** |
| total cost (NIHDI & co-payment) | **€7 207.96** | **€1 422.89** | **€5 488.85** | **€9 596.43** |
| total cost (NIHDI & co-payment + supplement device) | €33 818.39 | €1 422.89 | €32 099.28 | €36 206.86 |
| corrected** | **€27 754.93** | **€1 422.89** | **€26 035.82** | **€30 143.40** |
| total cost (all) | €33 898.03 | €1 461.13 | €32 118.95 | €36 218.96 |
| corrected** | **€27 834.57** | **€1 461.13** | **€26 055.49** | **€30 155.50** |
| **Details** | | | | |
| supplement for device (corrected)** | €20 546.97 | €0.00 | €20 546.97 | €20 546.97 |
| supplement for device (uncorrected) | €26 610.43 | €0.00 | €26 610.43 | €26 610.43 |
| cost day of intervention* | €5 816.72 | €1 873.65 | €3 497.35 | €8 787.81 |
| NIHDI | €5 465.87 | €1 539.56 | €3 497.35 | €7 497.04 |
| co-payment | €350.86 | €411.06 | €0.00 | €1 290.77 |
| cost before day of intervention, during hospitalisation* | €739.42 | €69.11 | €630.71 | €842.81 |
| NIHDI | €696.73 | €46.92 | €628.73 | €766.33 |
| co-payment | €42.69 | €30.58 | €1.98 | €76.48 |
| cost before day of intervention, outside hospitalisation* | €8.58 | €19.08 | €0.00 | €55.81 |
| NIHDI | €7.14 | €15.15 | €0.00 | €42.85 |
| co-payment | €1.44 | €4.32 | €0.00 | €12.96 |
| cost after day of intervention, during hospitalisation* | €212.19 | €232.70 | €27.72 | €805.95 |
| NIHDI | €197.20 | €208.13 | €27.72 | €725.28 |
| co-payment | €14.98 | €25.17 | €0.00 | €80.67 |
| cost after day of intervention, outside hospitalisation* | €431.04 | €660.17 | €0.00 | €2 078.05 |
| NIHDI | €396.14 | €653.94 | €0.00 | €2 032.68 |
| co-payment | €34.90 | €41.22 | €0.00 | €114.16 |
| supplements (exclusive device) | €23.34 | €9.44 | €12.10 | €45.07 |
| insurance | €0.00 | €0.00 | €0.00 | €0.00 |
| private payment | €56.31 | €168.92 | €0.00 | €506.77 |

* = NIHDI (National Institute for Health and Disability Insurance) & co-payments

** in the uncorrected supplement, the non-official price of €26 461.69 was included. Since a lower price of €20 398.23 was approved by the Ministry of Economics, this supplement was adjusted in our calculations.

**Table 5.5: Length of hospitalisation and cost information for homograft in a university hospital in Belgium**

| | mean | st.dev. | minimum | maximum |
|---|---|---|---|---|
| **General information** | | | | |
| length of hospitalisation (days) | **9.74** | **7.20** | **6** | **56** |
| total cost (NIHDI & co-payment) | **€12 234.66** | **€2 201.16** | **€9 738.35** | **€23 616.05** |
| total cost (all) | **€13 016.14** | **€3 181.77** | **€9 978.38** | **€29 629.24** |
| **Details** | | | | |
| cost of device | €2 672.30 | €613.52 | €901.29 | €6 054.15 |
| cost day of intervention (exclusive cost of device)* | €7 093.45 | €1 005.62 | €5 425.97 | €11 395.64 |
| NIHDI | €6 900.66 | €927.41 | €5 303.91 | €10 851.63 |
| co-payment | €192.79 | €200.14 | €0.00 | €801.55 |
| supplement | (€113.17) | (€191.96) | (€0.00) | (€771.64) |
| insurance | (€139.45) | (€249.01) | (€0.00) | (€862.27) |
| private payment | (€236.96) | (€930.05) | (€0.00) | (€4 583.13) |
| cost before day of intervention, during hospitalisation* | €675.97 | €304.59 | €365.26 | €2 054.82 |
| NIHDI | €645.06 | €297.87 | €341.78 | €2 008.41 |
| co-payment | €30.91 | €30.81 | €0.00 | €115.51 |
| supplement | (€19.23) | (€35.85) | (€0.00) | (€174.00) |
| insurance | (€18.76) | (€40.93) | (€0.00) | (€233.24) |
| private payment | (€3.06) | (€12.46) | (€0.00) | (€69.31) |
| cost before day of intervention, outside hospitalisation* | €353.88 | €1 078.94 | €0.00 | €7 039.21 |
| NIHDI | €333.43 | €1 067.13 | €0.00 | €6 978.01 |
| co-payment | €20.45 | €27.14 | €0.00 | €94.09 |
| supplement | (€1.82) | (€6.66) | (€0.00) | (€42.48) |
| insurance | (€20.03) | (€125.15) | (€0.00) | (€855.52) |
| private payment | (€77.62) | (€500.30) | (€0.00) | (€3 428.44) |
| cost after day of intervention, during hospitalisation* | €1 169.74 | €688.19 | €484.83 | €4 925.42 |
| NIHDI | €1 103.38 | €676.75 | €441.40 | €4 880.03 |
| co-payment | €66.36 | €56.17 | €0.00 | €211.99 |
| supplement | (€51.86) | (€123.41) | (€0.00) | (€701.14) |
| insurance | (€85.32) | (€208.80) | (€0.00) | (€995.91) |
| private payment | (€10.28) | (€35.42) | (€0.00) | (€209.29) |
| cost after day of intervention, outside hospitalisation* | €269.33 | €320.98 | €0.00 | €1 463.53 |
| NIHDI | €216.44 | €263.33 | €0.00 | €1 259.01 |
| co-payment | €52.89 | €64.80 | €0.00 | €262.17 |
| supplement | (€1.38) | (€9.41) | (€0.00) | (€64.50) |
| insurance | (€1.53) | (€10.49) | (€0.00) | (€71.94) |
| private payment | (€1.00) | (€4.78) | (€0.00) | (€23.85) |
| supplements | €187.46 | €262.54 | €0.00 | €1 094.85 |
| insurance | €265.10 | €503.62 | €0.00 | €2 421.40 |
| private payment | €328.92 | €1 077.06 | €0.00 | €4 861.73 |

* = NIHDI (National Institute for Health and Disability Insurance) & co-payments

## 5.2 COST EFFECTIVENESS OF PERCUTANEOUS HEART VALVES: A REVIEW OF THE LITERATURE

### 5.2.1 Methods

#### *5.2.1.1 Literature search strategy*

The search for the economic literature on the use of PHVs was performed by consulting various databases up to June 24, 2008. The CRD HTA and CDSR Technology Assessment databases were searched to retrieve HTA reports on this topic. The websites of HTA institutes mentioned on the INAHTA (International Network of Agencies for Health Technology Assessment) website and NICEs (National Institute for Health and Clinical excellence) website were also consulted. The NHS EED(CRD), Medline(OVID), EMBASE, and CDSR Economic Evaluation databases were searched. No restrictions on the time period and language were imposed. An overview of the search strategy and results are provided in appendix.

#### *5.2.1.2 Selection criteria*

All retrieved references were assessed against pre-defined selection criteria, in terms of population, intervention and design (Table 5.6), in a two-step procedure: initial assessment of the title, abstract, and keywords, followed by a full-text assessment of the selected references. When no abstract was available and the citation was unclear or ambiguous, consideration of the citation was directly made on the basis of full-text assessment. Reference lists of the selected studies were checked for additional relevant citations. This whole literature search and selection procedure was replicated by a second reviewer to assess the quality of this process and approve the literature selection. Only full economic evaluations, i.e. the studies comparing at least two alternative treatments in terms of costs and outcomes (see classification in appendix), were eligible.

**Table 5.6: Economic evaluation selection criteria**

| | Inclusion criteria | Exclusion criteria |
|---|---|---|
| Population | Patients with congenital heart disease and degeneration of a previously surgically constructed RVOT (group a) and patients with degenerative aortic stenosis (group b). | Other patient groups |
| Intervention | Percutaneous heart valve implantation: PPV for group a patients and PAV for group b. | Other interventions |
| Comparator | Conventional surgery and/or medical treatment | None |
| Design | Full economic evaluations (primary or secondary studies) | Cost description, cost comparison, etc. |

### 5.2.2 Results

Several manuscripts on PPV or PAV insertion were found on the websites of the following HTA institutes: ASERNIP-S, CADTH (evolved from the former CCOHTA (The Canadian Coordinating Office for Health Technology Assessment)), HAS, LBI, NICE, and NOKC. An overview of these references is provided in Table 5.7.

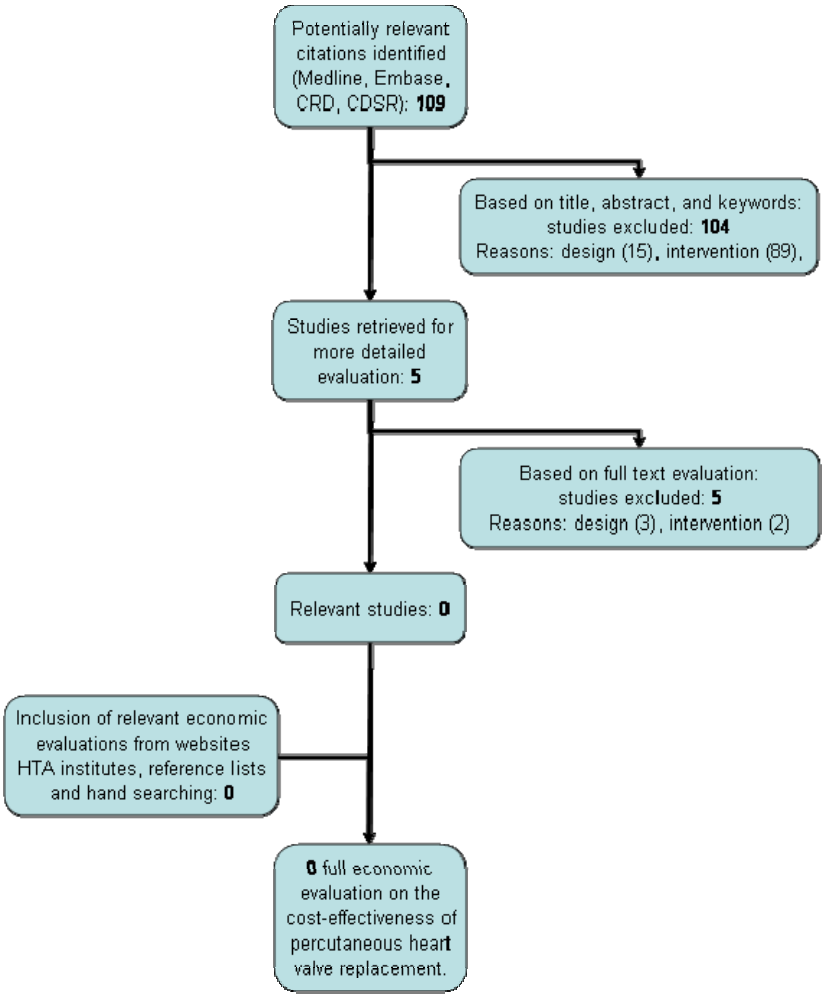
**Table 5.7: Reports/documents found on websites of HTA institutes**

| Institute | Report/document |
|---|---|
| ASERNIP-S | Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S). Horizon Scanning Technology Prioritising Summary: Percutaneous aortic valve replacement. 2007 (February).[78]<br>Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S). Horizon Scanning Technology Prioritising Summary: Percutaneous aortic valve replacement. 2007 (August).[57] |
| CADTH (formerly CCOHTA) | Canadian Coordinating Office for Health Technology Assessment (CCOHTA). Emerging Technology List: Percutaneous heart valve replacement. 2005 (June).[79] |
| HAS | Haute Autorité de Santé (HAS). Commission d'evaluation des produits et prestations, avis de la commission: EDWARDS SAPIEN 9000TFX, valve aortique péricardique bovine à implantation trans-apicale. 2007 (décembre).[80]<br>Haute Autorité de Santé (HAS). Commission d'evaluation des produits et prestations, avis de la commission: EDWARDS SAPIEN 9000TFX, valve aortique péricardique bovine à implantation transfémorale. 2007 (décembre).[81]<br>Haute Autorité de Santé (HAS). Évaluation des bioprothèses valvulaires aortiques implantées par voie rétrograde transfémorale et transapicale. 2008 (janvier). [56] |
| LBI | Ludwig Boltzmann Institut für Health Technology Assessment (LBI-HTA). Minimal-invasiver perkutaner Aortenklappenersatz: Systematischer Review. 2008 (März). Decision Support Document Nr. 18.[82]<br>Ludwig Boltzmann Institut für Health Technology Assessment (LBI-HTA). Perkutan implantierbare Pulmonalklappen bei angeborenen Herzfehlern des rechtsventrikul ren Ausflusstraktes: Systematischer Review. 2008 (März). Decision Support Document Nr. 10.[59] |
| NICE | NICE. Image-guided implantation of a new pulmonary valve. 2007. Understanding NICE guidance.[83]<br>NICE. Percutaneous pulmonary valve implantation for right vernticular outflow tract dysfunction. NICE; 2007 November 2007. Interventional procedure guidance 237.[72]<br>NICE. Catheter insertion of a new aortic valve to treat aortic stenosis. 2008. Understanding NICE guidance.[62]<br>NICE. Transcatheter aortic valve implantation for aortic stenosis. NICE; 2008 June 2008. Interventional procedure guidance 266.[71] |
| NOKC | Norderhaug, Krogstad, Ingebrigtsen, Søreide, Wiseth, Myhre, et al. Pasientvolum og behandlingskvalitet ved hjerte- og karsykdommer. Oslo: 2007. Rapport fra Kunnskapssenteret Nr 10–2007.[84] |

None of these HTA reports, however, included a full economic evaluation of the intervention concerned, neither under the form of a literature review, nor as a separate economic evaluation.

Our search in the other databases retrieved 109 unique references, after the exclusion of eight duplicates, which were assessed against our inclusion criteria. The flow chart of the selection process is presented in Figure 5.2. From these 109 references, 104 did not meet inclusion criteria based on title and abstract evaluation. The five remaining citations retained for full-text assessment were also excluded. In the end, no full economic evaluations on percutaneous heart valve replacement were identified.

**Figure 5.2: Identification and selection of studies**




CRD: Centre for Reviews and Dissemination; CDSR: Cochrane Database of Systematic Reviews; HTA: Health Technology Assessment

## 5.3 GATHERING (COST) INFORMATION IN TIME

Due to increasing health care expenditures and limited budgets, the acceptability and affordability of new expensive health technologies is often questioned. Information on the cost-effectiveness of new and apparently expensive treatment options may provide an answer to the question whether or not they offer 'value for money'. The percutaneous placement of aortic or pulmonary valves is a costly procedure, mainly due to the high cost of the device. The price for the pulmonary valve Melody™ from Medtronic was determined at €20 398.24 (incl. TAV) in Belgium. For the Edwards SAPIEN™ and Corevalve Revalving™ this was €20 398.24 and €19 610 (incl. TAV), respectively. Currently, however, no economic evaluation on this topic could be identified in the published literature.

We had the opportunity to read in confidentiality a transparent report on the cost-effectiveness for one of the aortic valves included in this report. From a clinical point of view, the model had a logical structure. However, the number of assumptions was very large both concerning the clinical input, cost data, QoL, and extrapolations. A number of assumptions were also very favourable for the new intervention and not always realistic. For example, the percentage of re-hospitalizations being 0% up to 3 years after the initial percutaneous valve procedure, while 100% of patients in the comparative medical treatment group were hospitalized in the long-term. Another example of strong assumptions was the distribution of patients over the four NYHA classes.

These were used in combination with utilities for these four classes to calculate QALYs. The distribution over the four classes was based on different studies for the different treatment groups and was assumed to remain stable for at least the second and third year in all subgroups, even though it could be expected that functional status would on average decrease as these old patients with several co-morbid conditions grow older. Also some methodological aspects were eligible for improvement, e.g. assuming all events to occur at the end of each time period (and deceased persons of course do not drop death exactly at the end of each period). More remarks were discussed with the authors of this model. In brief, in our opinion, results were hard to rely on since, next to some methodological remarks, almost no reliable input data were available at the moment of the analysis. The study only provided a hypothetical calculation of what the cost effectiveness of the intervention could be taking into account several rather optimistic and hypothetical assumptions. The main reason is that currently, there is not enough evidence available to implement in the economic models.

Timely availability of information is a particular issue. Concerning efficacy/effectiveness, the evaluation should not start too late. During the period when clinicians have no preference between the treatment options to be compared, they may be more inclined to ask patients to participate in trials; however, once clinicians come to prefer either the standard or the alternative treatment, they may feel ethically obliged to provide only the treatment that they believe to be the best.[85] On the other hand, the evaluation should not start too early. The existence of the clinical learning curve also influences the timing. Assessments made before clinicians have acquired enough skills in the new procedure may produce misleading findings on benefits and costs. Assessments may need to be postponed until clinicians have reached an appropriate point on the learning curve but this can usually only be recognised retrospectively, by which time clinicians may no longer be prepared to randomise patients.[85]

Cost-effectiveness analyses crucially depend on evidence of effectiveness and therefore always come later in the evaluation process of a technology. Healthcare decisions, however, are frequently needed in the early stages of a technology's life cycle. As a consequence, decision makers are sometimes in a position of having to take decisions without having adequate cost-effectiveness data at their disposal.[86] Nowadays, a wide range of criteria are of importance to decision makers including social and ethical impact, effect on patterns of healthcare demand, cost-effectiveness and other issues. Researchers could/should take this into account in the early phase of evidence gathering. With respect to the economic evaluation of interventions, gathering information useful for the economic evaluation could already be gathered early on. As such, postponing of decisions, due to a lack of information, could be prevented. In the following two parts, we make some general reflections about which information could be gathered to be able to calculate cost effectiveness and the budget impact. It is recognized that RCTs are in the first place set up to demonstrate safety and efficacy. However, it may be beneficial to collect some additional information in a clinical trial rather than having to collect this afterwards, which may be more time-consuming and costly.

### 5.3.1 Gathering information to be able to perform a full economic evaluation

With PHVs, we are dealing with an implant that in the near future probably will be the subject of an economic evaluation to support policy makers when taking a decision on whether or not to reimburse these implants. It is important that manufacturers are aware of this and currently (hopefully) are gathering data to support such an evaluation. Looking at the confidential model allowed us to list some important aspects necessary for a good economic evaluation in the future. These aspects were subdivided in three groups, i.e. variables with respect to effectiveness, costs, and quality of life.

One of the questions in an economic evaluation is whether or not life years are gained. Does the intervention improve short-, medium-, or long-term survival when compared to conservative management and/or surgery (depending on the in- and exclusion criteria of the population). In the short- and medium term, this starts with gathering information on the intra-operative and post-operative mortality.

Long-term data will by definition take more time to gather and (conservative) extrapolation will be needed to calculate the number of life-years gained over a longer time period than that of trials.

To be able to calculate incremental costs, the costs of the initial intervention, inclusive procedure related complications, should be considered. Not only should the costs for the initial intervention, but also the duration and costs of hospitalisation be taken into account. Furthermore, the costs linked to short-, medium-, and long-term complications with information on the number of re-hospitalisations and/or re-interventions are of importance. Data on follow-up events and treatment including physician visits (average number per patient/year), diagnostic examinations (type, average number per patient/year), and drug therapy are also important. Since open heart surgery is one of the possible comparators, the aspect of rehabilitation should not be forgotten. If costs are difficult to gather, the probabilities for these cost generators could be gathered so that afterwards national costs/charges can be attached.

One aspect often neglected when performing trials is the aspect of quality of life, which is influenced by the rehabilitation period after the procedure, the complications, re-interventions, etc. This is necessary to be able to calculate quality-adjusted life years (QALYs). Sometimes there are even no life-years gained and QoL is the main factor for measurements of incremental benefits. For example, patients who would be considered ineligible for aortic heart valve replacement surgery might be eligible for percutaneous valve replacement. For many patients in this group, the procedure may be considered palliative − it would improve quality of life rather than increase life expectancy.[55] QALYs are often calculated indirectly, e.g. by measuring the NYHA functional classes and measuring changes in these classes over time. QoL scores are then afterwards linked to these NYHA functional class.[87] However, when dealing with a population with severe symptomatic aortic stenosis who are classified as 'inoperable' because of their estimated high surgical risk, improving the NYHA functional class may not result necessarily in the same improvements in QoL due to the presence of other co-morbidities. As a result, for reasons of reliability, the direct measurement of QoL may be preferred, using a generic QoL instrument.

Next to these general aspects, other items such as the service life of the device are very important. Bioprostheses in general are known to have a limited service life, and the long-term effectiveness of PHVs (that are de facto bioprostheses) so far is unknown because long term studies are lacking.

The number of open heart surgeries during a patient's life may be limited and therefore reducing the number of open heart surgeries may have a great impact in a relatively young patient population. PPV in some patients may represent the only alternative to conservative treatment.

Furthermore, the impact on indirect costs such as school absenteeism or absence from work is also relevant in the younger patient population. Currently, reliable evidence based information on most of these items is lacking. With information on all these and more other aspects, transparent modelling with (conservative) extrapolation scenarios, will allow researchers to calculate reliable short-and medium or even long-term cost-effectiveness ratios.

### 5.3.2 Gathering information to be able to estimate the budget impact

To have a reliable estimate of the potential budget impact of PHV technology, not only should the higher initial costs of the intervention be taken into account, but also the influence on other costs in the short-, medium- and longer term. Some general thoughts on different costs are given in the previous part. Furthermore, it is clear that we need a good estimate of the number of patients eligible for the intervention. For percutaneous aortic valve replacement, very different estimates were found in different reports. For Belgium, estimates of about 250 patients up to 800 patients per year were found (Table 5.8). The manufacturer already indicated that this number could increase due to the ageing of the population.

Simple extrapolation of the estimates from other countries to the Belgian population results in even broader estimates, ranging from a minimum of 65 to a maximum of 850 patients. This, however, are only rough approximations.

Part of this population are inoperable patients with aortic stenosis, the others being high-risk operable patients. A different interpretation of inoperable or high-risk operable patients, due to the fact that an alternative for this group is available, may have a large influence on the number of patients being treated with the new intervention. As mentioned in the CCOHTA report, if the new intervention offers a clinical advantage or becomes an alternative to surgery, pressures for earlier percutaneous intervention in patients with valve dysfunction may be expected.[55]

**Table 5.8: Estimates for the number of patients eligible for PAV.**

| Country (Population)[a] | Estimated number of eligible patients for PAV. |
|---|---|
| Belgium (10.4 million) | Request Special Solidarity Fund (2008)[88]: one can reasonably estimate that the total number of patients in whom a percutaneous aortic valve implantation is required and justified is 250 per year for Belgium.<br><br>Edwards Lifesciences (2008)[89]: About 1 350 patients were not operated due to co-morbidities, 270 were treated surgically but need a replacement of the prosthesis, and another 290 patients were at high risk for surgical intervention. They estimated that about 7% in the first year up to 15% in the third year would be eligible for percutaneous aortic valve replacement or between 135 and 290 patients yearly.<br><br>Corevalve (2008): in theory, an estimated number of about 800 patients would probably be eligible for percutaneous aortic valve replacement. |
| Canada (32.5 million) | CCOHTA (2005)[55]: according to Dr. Philippe Pibarot, (Canada Research Chair in Valvular Heart Diseases; Department of Medicine, Laval University, Sainte Foy, QC), 200-300 patients would be eligible:<br>about 3% to 5% of Canadian patients (100 to 150 Canadians) with severe aortic stenosis, who undergo aortic valve replacement, are high risk patients because of their depressed left ventricular function and other comorbidities. These patients might eventually benefit from a less invasive procedure. In addition, another 100 to 150 Canadian patients who would be considered ineligible for aortic heart valve replacement surgery might be eligible for percutaneous valve replacement. |
| France (61.3 million) | HAS (2008)[56]: 600 per year.<br>The eligible population for transcutaneous aortic valve replacement could maximum be 5000 patients per year. However, not all patients that could not have conventional surgery are automatically eligible for transfemoral or transapical implantation. Furthermore, not all patients at high-risk are not necessarily contra-indicated for surgery. As such, experts estimate the minimum number to be 600 per year. |
| Upper Austria (1.3 million[b]) | LBI (2008)[82]: 30 patients for percutaneous aortic valve replacement |

a: source: World Health Organisation (http://www.who.int/countries); b: Source: http://en.wikipedia.org/wiki/Upper_Austria

The estimated population eligible for a PPV is much smaller than that for a PAV. In the initial request for reimbursement of the Melody™ heart valve,[90] the company expected 15 to 20 patients younger than 18 years of age to be eligible for this treatment in Belgium. A couple of months later the age restriction was left out and 40 to 45 patients per year would become eligible for this intervention.[91] With the current technology, Belgian experts expect that within the first years to come, less than 50 PPVs will be needed per year. This would result in a budget impact of about €1 million, just for the device, without taking into account any other extra costs or cost savings.

One can expect a gradual increase of the number of eligible patients, because as time goes by, more and more of those in whom a homograft has been surgically implanted, will present with a degenerated RVOT conduit. Beyond 10 to 15 years following a first surgical homograft implantation, an estimated 5% of patients will require a redo intervention per year. It can also be expected that improvements in the PPV technology, which use is currently limited to pulmonary annulus dimensions of 22 mm, will permit implantations in patients with wider pulmonary annuli, resulting in a wider range of patients being eligible for the technique (e.g. patients with pure pulmonary regurgitation).[xiii]

### *Key points*

- **The Minister of Economics approved a retail price of about €20 000 for the percutaneous devices. In contrast, the cost for a standard surgical valve is about €3 000. No clear justification for this higher price was available. Setting a justified and transparent price from the beginning is desirable.**
- **In a Belgian hospital, based on purely observational data:**
  **- the short-term costs (30 days before till 180 days after the intervention) for the NIHDI, patient co-payments, and the device were about €27750 for PPV implantation versus €12200 for homograft implantation.**
  **- the mean length of hospitalisation was less than 4 days versus almost 10 days for PPV and homograft implantation, respectively.**
- **There are no published economic evaluations on percutaneous pulmonary or aortic valve insertion.**
- **Currently, it is hard to perform a reliable economic evaluation because there are no clinical studies with comparable populations in the intervention and control group(s).**
- **Research should not only pay attention to effectiveness-related aspects. Information related to costs and quality of life is also important and could for certain aspects already be gathered in RCTs to be able to perform reliable economic evaluations in the (near) future. An example is the collection of QoL data using a generic instrument or the length of hospitalisation.**
- **It is not very clear how many patients would be eligible for PAV or PPV. For PAV, the inclusion criteria are not clear at all, and may influence this number to a large extent. For PPV implantation, the population is relatively small and, based on expert opinion, the estimated number would be less than 50 per year. Further research on the number of patients being eligible is necessary.**

[xiii] M. Gewillig, personal communication. Sept 18, 2008.

# 6 ORGANISATIONAL ISSUES

It is premature to discuss the organisational prerequisites for a nationwide PHV interventions program, because safety and long term effectiveness of the technology is not yet established. Moreover, especially as far as PAV is concerned, the target group of patients that may benefit from the procedure is unknown. So far, in published series patients were considered for PAV when they were inoperable or were at very high operative risk for conventional surgery. Risk estimation, especially in an elderly population, however, seems to be no easy task and patients deemed inoperable by one group of surgeons may be considered operable by others.[34] Moreover, it is not clear whether the high interventional mortality risk associated with PAV insertion is lower than the risk run by these patients if they had been treated by conventional surgery. Only careful performed randomised trials may give an answer to this question. In PPV, patient selection is less ambiguous and any patient with an indication for surgical RVOT revision is considered by Bonhoeffer et al. as a candidate for PPV.[40]

PHV obviously is a technically challenging procedure that can only be considered by clinicians and cardiology teams with special expertise. Only a few centres worldwide have substantial experience with the PAV, whereas published case series related to PPV virtually originate from one single operator. Some of these investigators report a learning curve in their procedural success. An improvement over time is reported by Webb et al. using the Edwards PAV when comparing outcomes in the initial 25 and subsequent 25 patients: procedural success increased from 76% to 96%.[32] In Grube's experience with the CoreValve PAV on the other hand, procedural success was similar in third generation 18F devices (n=36; success rate: 89%) as compared to second generation 21F valves (n=50; success rate: 88%).[37] A learning curve was also noticed by Bonhoeffer with the insertion of the Melody PPV. The incidence of procedural complications fell from 6% (3/50) in his first cohort to 2.9% (3/105) in the second cohort of patients. Redo interventions were needed in 29/50 (58%) of patients in the first cohort (median follow up 28 months) as opposed to 14/105 (13%) in the second (follow up ~2 years).[40]

A reduction in procedure related mortality has also been reported to be related to operator experience, although it is not clear whether this is due to improved skills or to a different patient selection. In Webb's series of Edwards PAV, there was a reduction of 30-day mortality over time: it was 16% in their initial 25 patients, falling to 8% in the second cohort of 25 patients.[32] In Grube's experience with the CoreValve PAV on the other hand, 30-day overall mortality was similar in third generation 18F devices (14%) as compared to second generation 21F valves (10%).[37] In 2006, the three first Belgian patients treated with PAV died shortly after the procedure, which lead the investigators to temporarily put their PAV interventions on hold.[92]

With respect to new surgical technologies, Wilson argues: "Use of new surgical technology has the potential to provide patients with the best possible care while reinforcing the professional vitality of the surgeon and the institution, boosting their image, and providing a competitive advantage. Conversely, that decision also has the potential to sully reputations, waste resources, and cause inadvertent harm to patients. Surgeons and institutions must guard against "going with the tide" in adopting a technology without solid evidence of its efficacy and superiority over alternatives. In the final analysis, a surgeon's skill and ability to perform a procedure well is unimportant, in fact irrelevant, if the procedure should not be done in the first place."[93]

### *Key point*

- **It is premature to discuss the organisational prerequisites for a nationwide PHV interventions program, as long as no hard effectiveness data have become available.**

# 7 DISCUSSION

## 7.1 PERCUTANEOUS AORTIC VALVE INSERTION

Currently, the position of PAV insertion within the management spectrum of aortic valve stenosis is unknown. Results from randomised controlled trials are not available and clinical data can only be deduced from observational studies. As shown in Table 7.2, most issues involving the use of PAV remain unanswered.

### 7.1.1 Appropriateness

The choice whether or not to correct (by surgery or PAV) a severe aortic stenosis is the result of a deliberation between the clinician and the well-informed patient, who have to trade-off the natural history of the AS, and the potential benefit of a correction of the valvular dysfunction. In younger symptomatic patients, evidence favours surgical AVR, because the natural history of aortic stenosis is dismal. Even in the elderly, surgical AVR can still be performed with acceptable mortality rates. Because surgical risk increases with age and even more so if co-morbidities (general frailty, lung disease, renal failure) are present, the less invasive PAV insertion has been developped in an attempt to reduce operative risk. However, in these high-risk patients, QoL and life expectancy are not only determined by the aortic valve disease as such. Age by itself and the natural history of the other conditions (that remain unaffected by cardiac surgery), bear upon survival and on QoL and should play a role in making a decision whether or not to proceed to a correction of the AS. With the development of the PAV, a choice could now be made between PAV and conventional surgery. Current evidence however does not provide reliable information to judiously trade off these alternatives.

"High-surgical-risk" and "operability" status are poorly defined, and the predictive impact of co-morbidities on postinterventional survival is not well studied in the field of valve intervention. In an editorial comment on PAV, it is contended that the term "high-risk" surgical patient is very broad and can accommodate virtually any situation.[12] There are no precise recommendations on the contraindications for surgery.[11] Walther argues that "we often perform conventional aortic valve surgery on such patients (i.e. high risk patients, deemed as inoperable) because we seldom deem aortic stenosis patients as inoperable."[67] The mortality risk for conventional AVR in most PAV series[32, 37, 67] is predicted by using the EuroSCORE, but several studies have shown that it poorly estimates mortality in patients undergoing valvular surgery, especially in high risk subjects.[13, 25, 27, 28, 60, 94-96] This is due to the fact that these high-risk patients represent only a small proportion of the index population from which the scores were elaborated. Moreover, high-risk patients form a particularly heterogeneous group in which it is difficult to capture all the comorbidities.[2] Finally, as discussed later, several conditions that are often encountered in elderly subjects are not taken into account when calculating the EuroSCORE (Figure 8.1).

Currently, it is not clear which elderly patients with substantial co-morbidity, and therefore a limited life expectancy, should be offered a correction of a symptomatic severe aortic stenosis. It is not clear if these patients fare better with PAV than with medical treatment or traditional surgical AVR. The latter aspect can only become clear when the results from an ongoing randomised controlled trial become available.

### 7.1.2 Feasibility

The most relevant message from registry data is that PAV insertion is feasible in 86-93% of attempts in recently published series. Unpublished data report success rates up to 100%.[54] These results have been obtained by experienced teams who noticed an apparent learning curve. Results from the initial antegrade technique (via the interatrial septum) were less favourable (75%) at least partly because of the very demanding nature of the procedure, which is one of the reasons why this approach has been largely abandoned.

With the retrograde approach, an improvement of procedural success from 76% in the initial 25 patients to 96% in the subsequent 25 patients has been reported with the Edwards PAV.[32] In Grube's experience with the CoreValve PAV on the other hand, procedural success was similar in third generation 18F devices as compared to second generation 21F valves (89 vs. 88%).[37]

### 7.1.3 Safety

Safety is a major issue in PAV insertion and includes both fatal and non-fatal complications.[2, 34, 68, 94] So far, patients with severe AS have been selected for PAV based on a consensus between cardiologists and cardiac surgeons that conventional surgery was excessively high in terms of anticipated mortality. Operative mortality in most series has been estimated quantitatively by means of the logistic EuroSCORE. Obviously, irrespective of treatment, prognosis is poor in an octogenarian with severe AS, deemed inoperable because of substantial co-morbidities. Hence it comes as no surprise that procedure related mortality for PAV was also high in published series.

In recent months, data from increasing numbers of patients treated with PAV, are presented at international meetings (Figure 8.3). Data presented at these meetings provide a way to compare currently reported safety aspects with those of the published data discussed earlier. Table 7.1 presents mortality data at 30 days and at 6 months after a PAV procedure as reported in relevant published series (Table 3.3) and registries presented at recent international meetings: EuroPCR08 (Barcelona, Spain, May 13-16, 2008), European Association for Cardio-Thoracic Surgery (EACTS) meeting (Lisbon, Portugal, September 2008) and TCT 2008 (Transcatheter Cardiovascular Therapeutics, Washington, October 2008). Some overlap between "published" and "presented data"[xiv] may exist. Data from series presented at recent meetings are obtained from grey literature and are not always completely identical among different sources. The data sources we drew upon to compose Table 7.1 are indicated in the table. Registries enrolling patients in which the transfemoral or the transapical approach was used were clustered in this table. Both early and intermediate term mortality figures are higher in transapical series as compared to series reporting transfemoral PAV insertion. This is at least partly due to patient selection, and related to the fact that the vascular status of patients treated by the transapical route is more impaired. Some interventionalists proceed to transapical PAV insertion only if the transfemoral approach is impossible because of insufficient vascular access. Transapically treated patients can thus be considered at a higher operative risk, which is also reflected in their higher EuroSCORE: 31.1 vs 24.0 in "published series" and 29.9 vs 25.4 in "presented series" respectively (Table 7.1).

[xiv] Series presented at 2008 cardiology meetings (Table 7.1) are further in the text referred to as "presented data" as opposed to "published data".

**Table 7.1: Mortality in PAV recipients: data extracted from published series and data presented at 2008 cardiology meetings.**

| | | n | 1 month | | 6 months | | Euro SCORE |
|---|---|---|---|---|---|---|---|
| | | | % | n | % | n | |
| **Most relevant recently published series (Table 3.3)§** | | | | | | | |
| **TRANSFEM** | Webb (Cribier Edwards) | 50 | 12,0 | 6 | 18,0 | 9 | 28,0 |
| | Grube (CoreValve - 2nd and 3d gen.) | 86 | 11,6 | 10 | | | 21,7 |
| | **SUBTOTAL** | **136** | **11,8** | **16** | | | **24,0** |
| **TRANSAP** | Walther (2008 single centre paper) | 50 | 8,0 | 4 | 26,1 | 13 | 27,6 |
| | Svensson (FDA feasibility study) | 40 | 22,5 | 9 | 41,3 | 17 | 35,5 |
| | **SUBTOTAL** | **90** | **14,4** | **13** | **32,9** | **30** | **31,1** |
| **ALL** | **TOTAL** | **226** | **12,8** | **29** | **27,9** | **39** | **26,8** |
| **Series presented at 2008 meetings** | | | | | | | |
| **TRANSFEM** | CoreValve 18F* | 536 | 8,1 | 43 | 21,0 | 113 | 23,1 |
| | REVIVAL 2* | 55 | 7,3 | 4 | 16,6 | 9 | 34,1 |
| | REVIVE 2* | 106 | 13,2 | 14 | 21,7 | 23 | 29,9 |
| | PARTNER EU*** | 54 | 8 | 4 | 10,0 | 5 | 24,7 |
| | SOURCE*** | 303 | 6,4 | 19 | | | 26,4 |
| | **SUBTOTAL** | **1054** | **8,1** | **85** | **20,0** | **150** | **25,4** |
| **TRANSAP** | SOURCE** | 309 | 11,6 | 36 | | | 30 |
| | PARTNER EU** | 67 | 18 | 12 | 45,0 | 30 | 33,5 |
| | TRAVERCE° | 168 | 14,9 | 25 | 30,0 | 50 | 26,9 |
| | REVIVAL 2°° | 40 | 17,6 | 7 | 35,8 | 14 | 35,5 |
| | **SUBTOTAL** | **584** | **13,7** | **80** | **34,5** | **95** | **29,9** |
| **ALL** | **TOTAL** | **1638** | **10,1** | **165** | **23,9** | **245** | **27,0** |

"Published data" are extracted from Table 3.3. Published studies are designated "relevant" if they include at least 40 patients and represent the most recent published paper from the specified investigator, with the longest reported follow-up data. § Time window of study available from Table 3.2. Registry acronyms: cfr,Figure 8.3 in appendix.

Data sources of studies presented at 2008 meetings: * Data presented at EuroPCR08 from Serruys[54]. ** Data from European Association for Cardio-Thoracic Surgery (EACTS) (Medscape website http://www.medscape.com/cardiology - October 2, 2008. *** Data from TCT2008 (Medscape website, October 14, 2008). ° Data from TCT2008 website (http://www.tctmd.com/default.aspx). °°Data from Dewey, TCT2008. "CoreValve 18F" refers to registry in which the corresponding device size is used.

The 30-day mortality rate, that most likely reflects procedure related mortality, is lower in recently presented transfemoral series (8.1 vs 11.8%) as compared to published series. This can partly be explained by improving skills and better technology, A stricter patient selection towards lower risk may also have a role in the lower operative mortality observed in recently presented series. This presumed lower operative risk is however not reflected by the similar EuroSCORE (26.8 vs 27.0) but it should be noted that a range of significant comorbidities are not included in the EuroSCORE.[67] It can be inferred from Figure 8.1 (appendix) that several conditions that are often encountered in an elderly population are not taken into account by the EuroSCORE: heart failure, diabetes mellitus, presence and degree of mitral regurgitation, arrhythmias, previous stroke, renal failure.

Nevertheless, even in recent series, where improving technical skills and technology performance might have attained "the flat of the learning curve", both procedure-related mortality rates and 6-month mortality figures remain high.

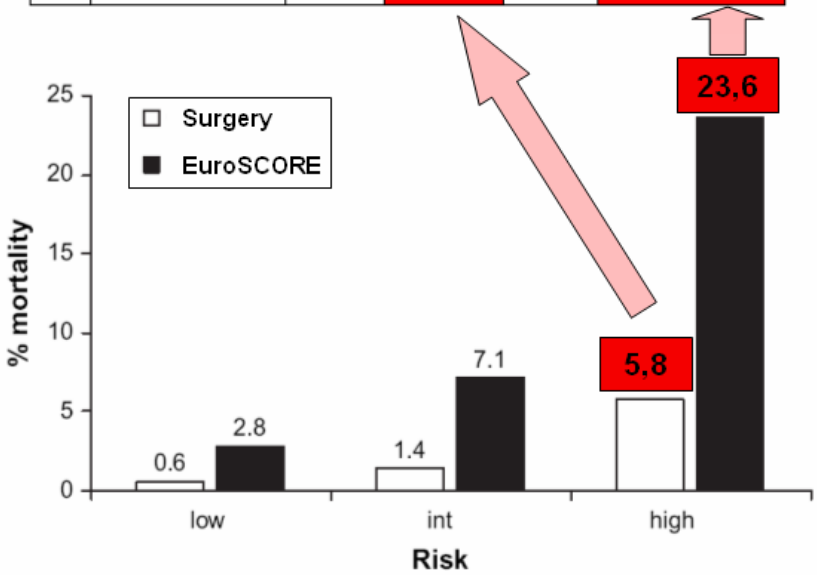
Especially perioperative mortality rates recently presented in transapical series were alarmingly high, amounting to a 17.6% early mortality in REVIVAL 2 and a 45.0% 6-month mortality in PARTNER EU.

These impressive procedure-related mortality rates should be compared with the operative risk patients are facing in conventional surgery. Reliable AVR related mortality data however are not available for the presumed target PAV population. In a substudy of the EHS on patients aged ≥75 years with severe AS, five of 100 (5%) died during the post-operative period.[4] In a literature review on results of AVR in the octogenarian, operative mortality of isolated AVR varied between 4.3 and 10.3%.[5] In a Belgian series of 220 consecutive octogenarians undergoing isolated AVR, operative mortality was 9%.[97] Very recently operative results of 1000 "minimally invasive" (i.e. parasternal approach or hemisternotomy) AVR were reported.[98] Among 160 patients of 80 years or older, undergoing isolated AVR, operative mortality rate was 1.9%, whereas predicted mortality by the STS (Society of Thoracic Surgeons) risk algorithm was 7.5%. Observations by Svensson et al. indicate that patients with aortic stenosis deemed inoperable by one group of surgeons may be considered operable by another. About half of the patients that were sent to this group as potential PAV candidates were further treated medically, 20% were treated with a PAV (9% mortality), 18% were treated surgically with no mortality at all and 11% were treated by means of balloon valvulopalsty.[34] In the French PAV series described by Descoutures, in 66 elderly patients referred for treatment of severe AS, 39 had a calculated operative risk of >20%.[60] Twelve were treated with PAV while from the remaining 27, four were "redirected" towards AVR. Two of them had severe coronary heart disease and underwent combined surgery (AVR+CABG). They all had an uneventful recovery.

Very recently, data from 1177 patients that underwent an isolated AVR between 2000 and 2006 were published.[28] In the highest risk tertile of patients, based on the logistic EuroSCORE, 30-day mortality was estimated at 23.6±14.8%, which sharply contrasted with an observed mortality of 5.8% (23 of 399 patients) (lower part of Figure 7.1). The authors conclude that an elevated EuroSCORE alone does not appropriately define a population for use of a PAV. Figure 7.1 shows EuroSCOREs and 1-month mortality rates from recently presented transfemoral PAV series (Table 7.1) and compares them with Brown's data. Whereas the EuroSCORE differs only slightly between the PAV and the AVR series, 1-month mortality is substantially higher in the former (8.1 vs 5.8%). This suggests that peri-operative mortality risk incurred by high-risk patients may be lower when they are treated by conventional surgery than by means of the putatively safer PAV. This further emphasizes that randomised controlled trials are badly needed to clarify the safety issue of PAV insertion.

**Figure 7.1: EuroSCORE predicted mortality versus observed mortality in recently presented transfemoral PAV series (upper part of figure), and in different risk subgroups of patients treated by conventional surgery (lower part).**

| | | n | Observed PAV procedural mortality | | Predicted surgical mortality (EuroSCORE) |
|---|---|---|---|---|---|
| | | | % | n | |
| TRANSFEMORAL | CoreValve 18F* | 536 | 8,1 | 43 | 23,1 |
| | REVIVAL 2* | 55 | 7,3 | 4 | 34,1 |
| | REVIVE 2* | 106 | 13,2 | 14 | 29,9 |
| | PARTNER EU*** | 54 | 8 | 4 | 24,7 |
| | SOURCE*** | 303 | 6,4 | 19 | 26,4 |
| | **SUBTOTAL** | **1054** | **8,1** | **85** | **25,4** |




Upper part of figure extracted from Table 7.1. Lower part copied and adapted from figure 3 in Brown[28].

From the above observations it is clear that one should be wary to predict operative mortality in elderly patients considered for AVR, based on risk scores obtained from historic observational data. Overestimation of risk may lead to inclusion in experimental treatment protocols of patients who could do well with conventional approaches[27] or to denying surgery in patients that may be suitable candidates.

Apart from mortality related to the procedure, safety issues of PAV also include non-fatal complications such as vascular injury at the access site, often requiring corrective surgery. Vascular complications occur especially when the transfemoral route is used, with an incidence of 10-15%. Stroke occurrence ranges from 3-10% in the transfemoral and 0-6% in the transapical approach.[2, 37] A residual paravalvular leakage of blood occurs in 10% of cases and the longer term impact of this remains unknown. A high incidence of atrioventricular block has been reported, necessitating permanent pacemaker implantation in up to a quarter of cases.[13] In a series of 50 patients in whom a PAV was inserted transapically, seven patients post-operatively required temporary renal replacement therapy, whereby three of these patients had pre-existing renal failure.[26]

Although data on an increasing number of patients are becoming available, they do not add to our understanding of the potential benefit and risks of this new technology. The methodological flaws prevailing in the initial series remain unaltered, i.e. the data presented are mere observational from selected and unrandomised patient groups.

### 7.1.4 Clinical effectiveness

Data on the clinical effectiveness of PAV insertion are scarce and based on observational studies only. Short term echocardiographic data, up to two years, in a limited number of patients, show a definite improvement of hemodynamic parameters. It is however not clear how this improvement in cardiac function can be translated to an improved overall well-being of the old and elderly subject that is hindered by severe co-morbidities and restricted in life due to general frailty. Scientific data on quality of life of patients that survived the procedure mostly is limited to improvements in the reported NYHA class. There is no information on QoL as measured with a generic instrument.

The long term durability of the PAV remains unknown. Given the limited life expectancy of patients currently considered for PAV, this may be less important for the time being. It might become an issue when the indication of PAV would be extended to younger and lower risk populations.

### 7.1.5 Cost effectiveness

There is not enough evidence on the efficacy or effectiveness of PAV implantation to be able to calculate the intervention's cost effectiveness. Further research is necessary. While performing this research, it might be interesting to think about which information could be gathered as input for economic evaluations. Trials are in the first place to gather evidence on the intervention's safety and efficacy. However, information on, for example, the duration of hospitalisation or the impact of QoL, measured with a generic instrument, could be gathered without much more effort. This might enable researchers to calculate the intervention's cost effectiveness in a reliable way in due time, i.e. when policy makers have to take a decision.

**Table 7.2. Appropriateness, feasibility, safety and effectiveness of PHV insertion. Summary of discussion.**

| Percutaneous aortic valve insertion (PAV) | | | | | | |
|---|---|---|---|---|---|---|
| | Procedure | | | Clinical effectiveness | | Cost Effect. |
| | Appropriateness | Feasibility | Safety | Early | Late | |
| **Device** | unknown; depends on effectiveness of PAV as compared to conventional surgery | feasible in 88-96% of attempts in the hands of experienced team | safety as compared to surgery unclear; 30-day mortality 10-15% in the hands of experienced team; | short term hemodynamic and clinical performance good | long term durability unknown (but a lesser issue, given the limited life expectancy of eligible patients) | lack of input data precludes reliable calculation of ICERs |
| **Patient** | choice depends on patient's preference whether to opt for conservative treatment or for correction of the valvular dysfunction (by any means) | | 6-month mortality 20-30% | unknown: as compared to surgery or medical therapy, it depends on co-morbidity related QoL and co-morbidity related life expectancy | | |

| Percutaneous pulmonary valve insertion (PPV) | | | | | | |
|---|---|---|---|---|---|---|
| | Procedure | | | Clinical effectiveness | | Cost Effect. |
| | Appropriateness | Feasibility | Safety | Early | Late | |
| **Device** | unknown; depends on effectiveness of PPV as compared to conventional surgery | feasible in 97% of attempts in the hands of one single operator | early mortality 1,3% in single operator experience | short term hemodynamic performance good | long term durability of the valve unknown | lack of input data precludes reliable calculation of ICERs |
| **Patient** | conservative treatment is no option in symptomatic patients; in asymptomatics, timing of the intervention (by any means) is unclear | | long term patient survival unclear | long term effectiveness in postponing surgery unknown | | |

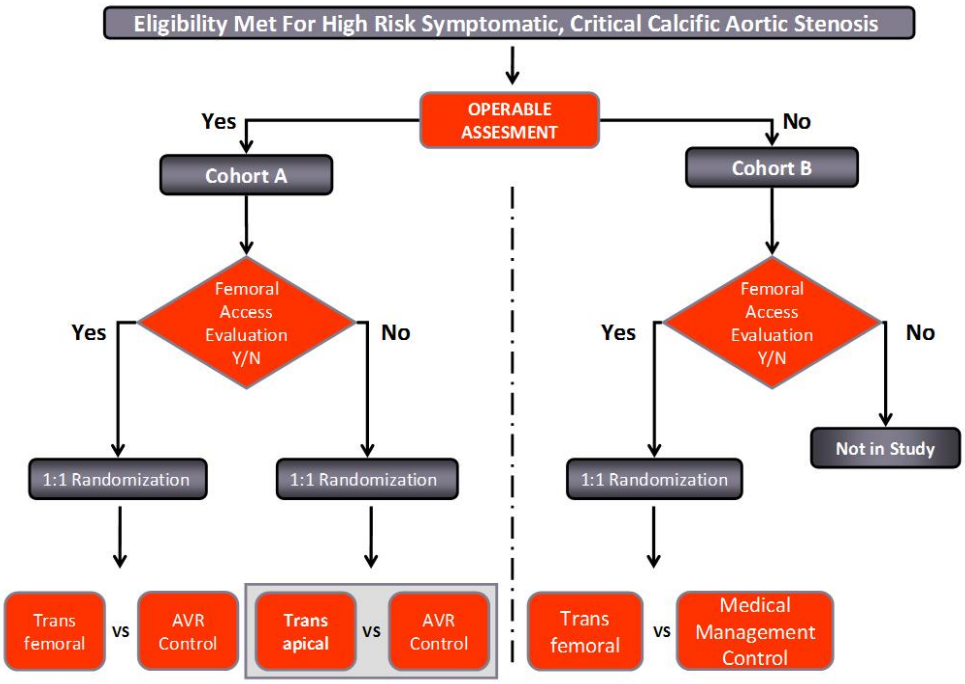
### 7.1.6 Scientific evaluation

In order to strengthen the evidence base of an emerging technology, either an RCT or an observational trial with longitudinal data registry are the main research designs.[42] The latter methodology can only be preferred if an RCT is impossible because of practical constraints. In the majority of invasive emerging technologies, this will however not be the case. Uncontrolled diffusion of a new experimental technology without evidence that more benefit than harm is invoked to patients, can be coined as unethical behaviour.[42]

So far, no RCTs on the use of any PHV has been completed. The United States' FDA imposes strict requirements before medical devices such as percutaneous heart valves can be placed on the market. First, reasonable assurance of feasibility and preliminary safety have to be demonstrated.[43] An investigational device exemption (IDE) can than be provided to allow the investigational device to be used in a clinical study in order to collect safety and effectiveness data required to support a so-called "pre-market approval" (PMA) application which is mandatory for class III devices, the highest risk class. For the Edwards Sapien PAV, an IDE has been granted for use of the device in the currently ongoing pivotal randomised controlled trial, the PARTNER (Placement of AoRTic TraNscathetER Valve Trial) trial, also sometimes referred to as the "PARTNER US" or the "PARTNER IDE" trial (ClinicalTrials.gov identifier NCT00530894). It is a randomised, open label trial that is sponsored by Edwards Lifesciences. The aim of the study is to evaluate the safety and efficacy of transapical and transfemoral delivery and implantation of the Edwards Sapien PAV in symptomatic adult patients with severe, valvular aortic stenosis, who are high risk candidates for routine open heart surgery. In a first cohort that is constituted of patients at high operative risk randomised to trans-femoral PAV, trans-apical PAV or conventional surgery, the primary outcome is freedom from death at 1 year (non-inferiority). The second cohort is composed of inoperable patients who are randomised to trans-femoral PAV or to medical treatment. Here, the primary endpoint is overall survival (superiority) (Figure 7.2) QoL measures would be taken at baseline, 30 days, 6 months, and 1 year. Participating centres are located in the US (15), Canada (3) and Germany (1). The trial started recruitment in April 2007 and aims to include 1040 patients. Obviously this is not a blind trial, and given the relative short life expectancy of the patients that will be enrolled (due to advanced age and co-morbidities), one can expect interim results of this trial within 1 or 2 years even though the estimated completion date of this trial is September 2014.

It should be noted that ambiguity may arise resulting from the misleadingly homonymic labelling of the European observational "PARTNER EU" study, which is merely a **registry** of patients treated with the Edwards Sapien PAV within Europe. Therefore, in order to avoid confusion, the United States based **RCT** often is referred to as the "PARTNER US" or the "PARTNER IDE" trial.

**Figure 7.2: Design of the PARTNER-IDE randomised controlled trial.**




From: Patrick W Serruys: Transcatheter aortic valve implantation: a state-of-the-art . EuroPCR08, Wednesday 14th May, 2008 (http://www.europcronline.com/fo/planning/event/europcr/consult_event.php?idCongres=4&id=4049)

During the recent TCT 2008 meeting, CoreValve announced its intention to start a randomised trial in 2009. The trial would be dubbed the Percutaneous Aotic Valve Intervention Study (PAVIS) and would enrol 1100 patients at 30 centres, including five in Canada and Europe. It would encompass an inoperable arm against medical therapy and a high-risk surgery arm against PAV.[99]

### *Key points*

- **It is not clear for which patients PAV is an appropriate alternative as compared to a conservative therapy or conventional surgery.**
- **The currently available data suggest that PAV insertion is feasible and provides at least short term (6 months-1 year) hemodynamic and clinical improvement in patients with severe AS at high risk for surgery that underwent a successful PAV insertion. However, it is not clear whether PAV performs better in improving a patient's life expectancy or QoL as compared to other treatment strategies.**
- **"High-surgical-risk" and "operability" status are poorly defined concepts and complicate the interpretation of outcomes from observational data. Risk prediction by means of EuroSCORE severely overestimates operative risk incurred by patients that are contemplated for PAV.**
- **Safety issues, demonstrated by a procedure related mortality rate (30-days) of 6.4-13.2% in transfemoral series, and 8.0-22.5% in transapical series, represent a major drawback for implementation of this technology. Early procedural mortality of PAV insertion may be higher than the risk incurred by conventional surgery.**
- **Six month mortality of these patients is very high, and ranges from 10-21.7% in transfemoral series and 26.1-45.0% in transapical series.**
- **The intervention's cost effectiveness can not be calculated reliably because no objective input data are available.**
- **Although data from an increasing number of patients enrolled in registries become available, these do not add to our understanding of the performance of this new technology in terms of its benefit and risks.**
- **The ongoing PARTNER-IDE RCT (= PARTNER US) is expected to clarify (1) if patients who are inoperable are better off with PAV than with medical treatment, and (2) if patients at high risk for surgery have a lower risk with PAV than with conventional AVR.**

## 7.2 PERCUTANEOUS PULMONARY VALVE INSERTION

### 7.2.1 Appropriateness

As discussed earlier, patients with congenital heart defects often require a provisional surgical repair early in life. This life-saving intervention commonly creates pulmonary valve incompetence for which later on, a more definitive operation is needed ("revalving"), consisting of the construction of a valved conduit between the right ventricle and the pulmonary artery. The lifespan of these homografts is much shorter than that of the patients receiving them, due to calcification of the valve, thereby making re-interventions later unavoidable.[16, 17] To prolong the lifespan of the conduit, endovascular stenting of the calcified valve has been developed, leading to a delay in conduit replacement for an average of 2.5 to 4 years.[19] In the end, replacement of the originally implanted graft will be needed, for symptomatic reasons and/or in order to try to avoid the development of right ventricular failure or ventricular arrhythmias.[100] In symptomatic patients, the appropriateness of a correction of the degenerated RVOT conduit (whether by conventional surgery or by means of a PPV) stands firm. In asymptomatic patients, the optimal timing of a correction is not clear, and standard practice involves watchful follow-up of patients until an intervention is deemed necessary, based on the onset of symptoms, or based on indirect parameters from electrocardiogram, echocardiography and exercise testing.[22]

It is estimated that in Belgium, 40-50 patients per year could benefit from the currently available PPV technology.

### 7.2.2 Feasibility

In their most recent article, Bonhoeffer et al. report on the feasibility of PPV insertion in 163 patients that were considered candidates for RVOT surgery.[40] Based on the morphologic data, 8 patients were excluded for the PPV procedure, because of unfavourable RVOT dimensions or a risk of coronary artery compression. Of 155 attempts for PPV insertion, the procedure was successful in 150 cases (97%).

### 7.2.3 Safety

In Bonhoeffer's series of 155 patients, there were no direct procedure related deaths. Two patients in whom the procedure was undertaken because of cardiogenic shock, died early[40], resulting in an early mortality of 2 patients (1.3%). During later follow-up, two patients died suddenly at 8 and 35 months.

Complications occurred in 12 patients (7.7%). In 5 of these patients, early surgical explantation of the PPV was needed because of dislodgement, homograft rupture, coronary artery obstruction or pulmonary artery obstruction. One other patient required surgery for bleeding after homograft rupture and one patient was resuscitated after homograft rupture but recovered. The incidence of procedural complications fell from 6% in the first cohort of 50 cases to 2.9% in the second cohort of 105 patients.

### 7.2.4 Clinical effectiveness

On echocardiography, PPV competence was well maintained during follow-up (median 28.4 months). Valve regurgitation was absent or trivial in 80% of cases at 36 months. Within 30 months after PPV insertion, 25% of patients needed a repeat intervention, in half of the cases a second ("valve-in-valve") PPV and in the other half a surgical valve implantation.[40] A learning curve was noted as far as the need for explantation of the PPV was concerned: of the first 50 patients, 16 underwent device explantation compared with 5 patients in the second cohort of 105 patients. Stent fracture–free survival at 1 year was 85.1%; at 2 years, 74.5%; and at 3 years, 69.2%. These stent fractures used to pose a problem,[20] but pre-stenting of the RVOT before introducing the PPV is reported to solve this problem.[101]

It is not clear to what extent PPV can postpone future RVOT surgery, because device longevity and optimal timing of the procedure are not known. As a result, the impact of the technology on life expectancy and QoL is uncertain. Ideally, an RCT could provide evidence, but given the small number of eligible patients, this should be undertaken on an international (European) level. No such trials are currently under way.

### 7.2.5 Cost effectiveness

There is not enough evidence on the efficacy or effectiveness of PPV implantation to be able to calculate the intervention's cost effectiveness. In the short term, the costs of PPV implantation are clearly higher in comparison to homograft implantation. It is not clear what the influence on costs would be in the long-term. Further research on effectiveness is necessary in the first place. Doing so, it could be wise to gather already input data that may be useful for economic evaluations.

### 7.2.6 Scientific evaluation

As discussed higher, evidence for the implementation of an emerging technology into clinical practice should preferentially be based on an RCT. To our knowledge, no such RCT has been planned to assess the efficacy and (cost-)effectiveness of PPV. It may be difficult to organise such an RCT based on patients selected from one single country because of the limited number of eligible patients; it is estimated that yearly no more than 50 patients would be candidates for PPV insertion in Belgium. However, a cross-border trial encompassing the European Union could offer a solution.

*Key points*

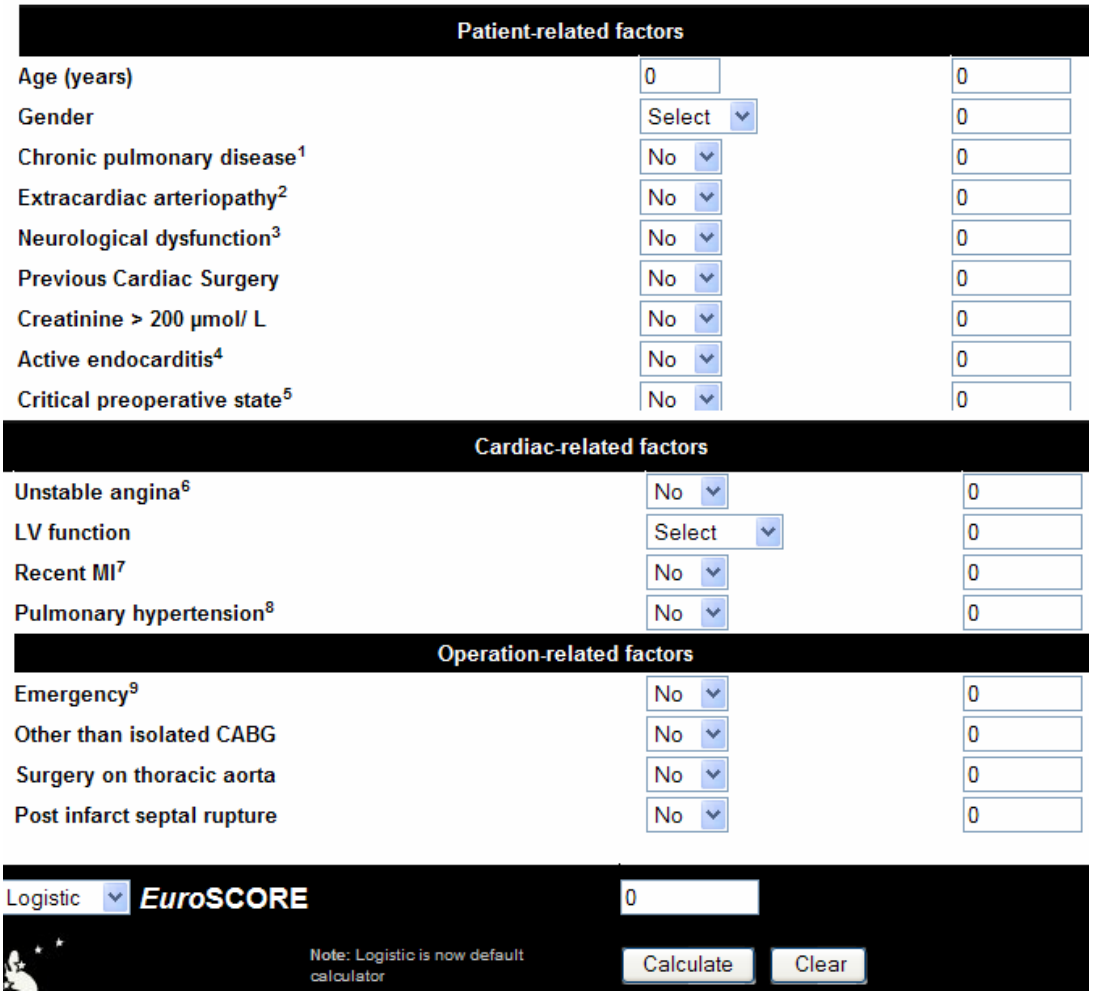
- **A conservative (i.e. medical) treatment is no option in symptomatic patients with a degenerated pulmonary conduit. In asymptomatic patients, the optimal timing for a correction (whether surgically or percutaneously) is unknown.**
- **The feasibility and safety of PPV insertion is excellent, at least in the hands of one operator.**
- **Short term hemodynamic and clinical performance is good. Long term durability of the valve is not known. Long term effectiveness postponing future surgery is unknown. Unfortunately, no RCTs are planned to resolve these questions.**
- **With current available input data, no reliable incremental cost-effectiveness ratio can be calculated for PPV implantation.**

# 8 APPENDIX

# APPENDIX 1: EUROSCORE

EuroSCORE provides a method of predicting the operative mortality for patients undergoing cardiac surgery. Two risk calculators are available on the website of EuroSCORE (http://www.euroscore.org): the simple additive EuroSCORE and the full logistic EuroSCORE. The full logistic version reportedly produces a more accurate risk prediction than the simpler additive model. Predicted mortality is calculated as described in Roques et al.[102] The clinical parameters that are taken into account in order to calculate the EuroSCORE are depicted in Figure 8.1.

**Figure 8.1. Calculation of the logistic EuroSCORE (http://www.euroscore.org/calc.html)**



# APPENDIX 2: REVIEW ECONOMIC LITERATURE

## PUBLISHED LITERATURE – SEARCH STRATEGY

***Search for cost-effectiveness studies***

On June 24, 2008, the websites of HTA institutes (Table 8.1) and following databases were searched: Medline, Embase, Centre for Reviews and Dissemination (CRD) databases (NHS Economic Evaluation Database (NHS EED) and Health Technology Assessments (HTA)), and Cochrane Database of Systematic Reviews (CDSR) (Technology Assessments and Economic Evaluations). The following five tables (Table 8.2 to Table 8.6) provide an overview of the search strategy.

**Table 8.1: List of INAHTA member websites searched for HTA reports**

| Agency | Country |
|---|---|
| AETMIS - Agence d´Évaluation des Technologies et des Modes d´Intervention en Santé | Canada |
| AETS - Agencia de Evaluación de Tecnologias Sanitarias | Spain |
| AETSA - Andalusian Agency for Health Technology Assessment | Spain |
| AHRQ - Agency for Healthcare Research and Quality | USA |
| AHTA - Adelaide Health Technology Assessment | Australia |
| AHTAPol - Agency for Health Technology Assessment in Poland | Poland |
| ASERNIP-S - Australian Safety and Efficacy Register of New Interventional Procedures -Surgical | Australia |
| AVALIA-T - Galician Agency for Health Technology Assessment | Spain |
| CADTH - Canadian Agency for Drugs and Technologies in Health | Canada |
| CAHTA - Catalan Agency for Health Technology Assessment and Research | Spain |
| CDE - Center for Drug Evaluation | Taiwan |
| CEDIT - Comité dÉvaluation et de Diffusion des Innovations Technologiques | France |
| CENETEC - Centro Nacional de Excelencia Tecnológica en Salud Reforma | Mexico |
| CMT - Center for Medical Technology Assessment | Sweden |
| CRD - Centre for Reviews and Dissemination | United Kingdom |
| CVZ - College voor Zorgverzekeringen | The Netherlands |
| DACEHTA - Danish Centre for Evaluation and Health Technology Assessment | Denmark |
| DAHTA @DIMDI - German Agency for HTA at the German Institute for Medical Documentation and Information | Germany |
| DECIT-CGATS - Secretaria de Ciëncia, Tecnologia e Insumos Estratégicos, Departamento de Ciência e Tecnologia | Brazil |
| DSI - Danish Institute for Health Services Research | Denmark |
| FinOHTA - Finnish Office for Health Care Technology Assessment | Finland |
| GR - Gezondheidsraad | The Netherlands |
| HAS - Haute Autorité de Santé | France |
| HSAC - Health Services Assessment Collaboration | New Zealand |
| HTA Malaysia - Health Technology Assessment Section, Ministry of Health Malaysia | Malaysia |
| IAHS - Institute of Applied Health Sciences | United Kingdom |
| ICTAHC - Israel Center for Technology Assessment in Health Care | Israel |
| IECS - Institute for Clinical Effectiveness and Health Policy | Argentina |
| IHE - Institute of Health Economics | Canada |
| IMSS - Mexican Institute of Social Security | Mexico |
| IQWiG - Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen | Germany |
| KCE - Belgian Federal Health Care Knowledge Centre | Belgium |
| LBI of HTA - Ludwig Boltzmann Institut für Health Technonoly | Austria |

| | |
|---|---|
| Assessment | |
| MAS - Medical Advisory Secretariat | Canada |
| MSAC - Medicare Services Advisory Committee | Australia |
| MTU-SFOPH - Medical Technology Unit - Swiss Federal Office of Public Health | Switzerland |
| NCCHTA - National Coordinating Centre for Health Technology Assessment | United Kingdom |
| NHS QIS - Quality Improvement Scotland | United Kingdom |
| NHSC - National Horizon Scanning Centre | United Kingdom |
| NOKC - Norwegian Knowledge Centre for Health Services | Norway |
| OSTEBA - Basque Office for Health Technology Assessment | Spain |
| SBU - Swedish Council on Technology Assessment in Health Care | Sweden |
| UETS - Unidad de evaluacíon Technologias Santarias | Spain |
| VATAP - VA Technology Assessment Program | USA |
| VSMTVA - Health Statistics and Medical Technologies State Agency | Latvia |
| ZonMw - The Medical and Health Research Council of The Netherlands | The Netherlands |

**Table 8.2: Search strategy and results for CRD**

| | | | |
|---|---|---|---|
| **Date** | 24/06/2008 | | |
| **Database** | CRD HTA & CRD NHS EED | | |
| **Date covered** | No restrictions | | |
| **Search Strategy** | **#** | **Search History** | **Results** |
| | 1 | percutaneous OR transcutaneous OR transcatheter OR transapical OR trans AND apical OR trans AND catheter OR cribier OR corevalve | 1101 |
| | 2 | MeSH Heart Valve Prosthesis EXPLODE | 20 |
| | 3 | MeSH Heart Valve Prosthesis Implantation EXPLODE | 19 |
| | 4 | #2 or #3 | **38** |
| | 5 | MeSH Aortic Valve EXPLODE | 11 |
| | 6 | MeSH Aortic Valve Stenosis EXPLODE | 8 |
| | 7 | MeSH Aortic Valve Insufficiency EXPLODE | 5 |
| | 8 | #5 or #6 or #7 | 22 |
| | 9 | MeSH Pulmonary Valve EXPLODE | 1 |
| | 10 | MeSH Pulmonary Valve Insufficiency EXPLOD | 0 |
| | 11 | MeSH Pulmonary Valve Stenosis EXPLODE | 2 |
| | 12 | #9 or #10 or #11 | 3 |
| | 13 | #8 or #12 | 24 |
| | 14 | #1 and #4 and #13 | 0 |
| **Note** | The less restrictive search #4 was selected. As such, 38 references were found in CRD, of which **5** were from the **HTA** database and **21** from the **NHS EED** database. | | |

**Table 8.3: Search strategy and results for Medline (OVID) (part I)**

| | | | |
|---|---|---|---|
| **Date** | 24/06/2008 | | |
| **Database** | Medline (OVID) | | |
| **Date covered** | 1996 to June Week 2 2008 | | |
| **Search Strategy** | **#** | **Search History** | **Results** |
| | 1 | economics/ | 4576 |
| | 2 | exp "Costs and Cost Analysis"/ | 75806 |
| | 3 | "Value of Life"/ec [Economics] | 166 |
| | 4 | Economics, Dental/ | 111 |
| | 5 | exp Economics, Hospital/ | 6904 |
| | 6 | Economics, Medical/ | 601 |
| | 7 | Economics, Nursing/ | 397 |
| | 8 | Economics, Pharmaceutical/ | 1545 |
| | 9 | 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 | 83364 |
| | 10 | (econom$ or cost$ or pric$ or | 185813 |

| | | | |
|---|---|---|---|
| | | pharmacoeconomic$).tw. | |
| | 11 | (expenditure$ not energy).tw. | 6858 |
| | 12 | (value adj1 money).tw. | 5 |
| | 13 | budget$.tw. | 6624 |
| | 14 | 10 or 11 or 12 or 13 | 192348 |
| | 15 | 9 or 14 | 226721 |
| | 16 | letter.pt. | 314192 |
| | 17 | editorial.pt. | 139211 |
| | 18 | historical article.pt. | 78404 |
| | 19 | 16 or 17 or 18 | 525425 |
| | 20 | 15 not 19 | 214670 |
| | 21 | Animals/ | 1679198 |
| | 22 | human/ | 4529608 |
| | 23 | 21 not (21 and 22) | 1121752 |
| | 24 | 20 not 23 | 197691 |
| | 25 | (metabolic adj cost).ti,ab,sh. | 286 |
| | 26 | ((energy or oxygen) adj cost).ti,ab,sh. | 959 |
| | 27 | 24 not (25 or 26) | 196756 |
| | 28 | exp aortic valve/ or exp pulmonary valve/ | 7041 |
| | 29 | (percutaneous or transcutaneous or transcatheter or transapical or trans apical or trans catheter or cribier or corevalve).mp. [mp=title, original title, abstract, name of substance word, subject heading word] | 51049 |
| | 30 | 28 and 29 | 217 |
| | 31 | 27 and 30 | 3 |
| | 32 | 27 and 28 | **67** |
| **Note** | Search strategy #31 was too stringent resulting in only three references. A broader search strategy (#32) was preferred too minimize the chance that references were missed. | | |

**Table 8.4: Search strategy and results for Medline (OVID) (part II)**

| **Date** | 24/06/2008 | | |
|---|---|---|---|
| **Database** | Medline (OVID), In-Process & Other Non-Indexed Citations | | |
| **Date covered** | No restrictions | | |
| **Search Strategy** | **#** | **Search History** | **Results** |
| | 1 | cost$.mp. [mp=title, original title, abstract, name of substance word, subject heading word] | 14332 |
| | 2 | economic$.mp. [mp=title, original title, abstract, name of substance word, subject heading word] | 6165 |
| | 3 | budget$.mp. [mp=title, original title, abstract, name of substance word, subject heading word] | 762 |
| | 4 | expenditure$.mp. [mp=title, original title, abstract, name of substance word, subject heading word] | 1349 |
| | 5 | 1 or 2 or 3 or 4 | 20371 |
| | 6 | (percutaneous or transcutaneous or transcatheter or transapical or trans apical or trans catheter or cribier or corevalve).mp. [mp=title, original title, abstract, name of substance word, subject heading word] | 3859 |
| | 7 | heart valve.mp. [mp=title, original title, abstract, name of substance word, subject heading word] | 147 |
| | 8 | aortic valve.mp. [mp=title, original title, abstract, name of substance word, subject heading word] | 694 |
| | 9 | pulmonary valve.mp. [mp=title, original title, abstract, name of substance word, subject heading word] | 113 |
| | 10 | 7 or 8 or 9 | 913 |
| | 11 | 6 and 10 | 76 |
| | 12 | 5 and 11 | **2** |
| **Note** | | | |

**Table 8.5: Search strategy and results for EMBASE**

| | | | |
|---|---|---|---|
| **Date** | 25/06/2008 | | |
| **Database** | EMBASE | | |
| **Date covered** | No restrictions | | |
| **Search Strategy** | **#** | **Search History** | **Results** |
| | 1 | socioeconomics'/exp | 107905 |
| | 2 | 'cost benefit analysis'/exp | 47553 |
| | 3 | 'cost effectiveness analysis'/exp | 55274 |
| | 4 | 'cost of illness'/exp | 8773 |
| | 5 | 'cost control'/exp | 32608 |
| | 6 | 'economic aspect'/exp | 760949 |
| | 7 | 'financial management'/exp | 188926 |
| | 8 | 'health care cost'/exp | 130140 |
| | 9 | 'health care financing'/exp | 9190 |
| | 10 | 'health economics'/exp | 414957 |
| | 11 | 'hospital cost'/exp | 17679 |
| | 12 | ('finance'/exp) OR ('funding'/exp) OR (fiscal) OR (financial) | 125500 |
| | 13 | 'cost minimization analysis'/exp | 1354 |
| | 14 | estimate*:ti,ab,de,cl | 358808 |
| | 15 | cost*:ti,ab,de,cl | 400220 |
| | 16 | variable*:ti,ab,de,cl | 354386 |
| | 17 | unit*:ti,ab,de,cl | 1355775 |
| | 18 | '#15 *4 #14' OR '#14 *4 #15' | 188437 |
| | 19 | '#15 *4 #16' OR '#16 *4 #15' | 188531 |
| | 20 | '#15 *4 #17' OR '#17 *4 #15' | 78958 |
| | 21 | #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #18 OR #19 OR #20 | 1198067 |
| | 22 | 'heart valve prosthesis'/exp | 22525 |
| | 23 | percutaneous OR transcutaneous OR transapical OR 'trans apical' OR transcatheter OR 'trans catheter' OR cribier OR corevalve | 109796 |
| | 24 | #22 AND #23 | 333 |
| | 25 | #21 AND #24 | **20** |
| **Note** | | | |

**Table 8.6: Search strategy and results for CDSR**

| | | | |
|---|---|---|---|
| **Date** | 25/06/2008 | | |
| **Database** | CDSR | | |
| **Date covered** | No restrictions | | |
| **Search Strategy** | **#** | **Search History** | **Results** |
| | 1 | MeSH descriptor Heart Valve Prosthesis explode all trees | 347 |
| | 2 | MeSH descriptor Heart Valve Prosthesis Implantation explode all trees | 232 |
| | 3 | percutaneous OR transcutaneous OR transcatheter OR transapical OR trans apical OR trans catheter OR cribier OR corevalve | 7273 |
| | 4 | (#1 OR #2) | 528 |
| | 5 | (#3 AND #4) | **4** |
| **Note** | Of these 4 references, there was **one** Technology Assessments and **one** Economic Evaluations | | |

### *Results of search strategy*

Several manuscripts were found on the websites of the following HTA institutes: ASERNIP-S, CADTH (evolved from the former CCOHTA (The Canadian Coordinating Office for Health Technology Assessment)), HAS, LBI, NICE, and NOKC. A total of 117 papers were identified in several databases: 69 with Medline, 20 with Embase, 26 with the CRD NHS EED and HTA databases, and 2 from the Cochrane Database of Systematic Reviews (Technology Assessments and Economic Evaluations) (Table 8.7). After removing 8 duplicates, 109 articles were left.

**Table 8.7: search for cost-effectiveness studies: summary**

| Database | Search date or Years included | References identified |
|---|---|---|
| MEDLINE | 1996 to June Week 2 2008 | 67 |
| MEDLINE In-Process & Other Non-Indexed Citations | June 24, 2008 | 2 |
| EMBASE | June 24, 2008 | 20 |
| CRD | June 24, 2008 | |
| NHS EED | | 21 |
| HTA | | 5 |
| CDSR | June 25, 2008 | |
| Technology Assessments | | 1 |
| Economic Evaluations | | 1 |
| Total references identified | | 117 |
| Duplicates | | 8 |
| Total | | **109** |

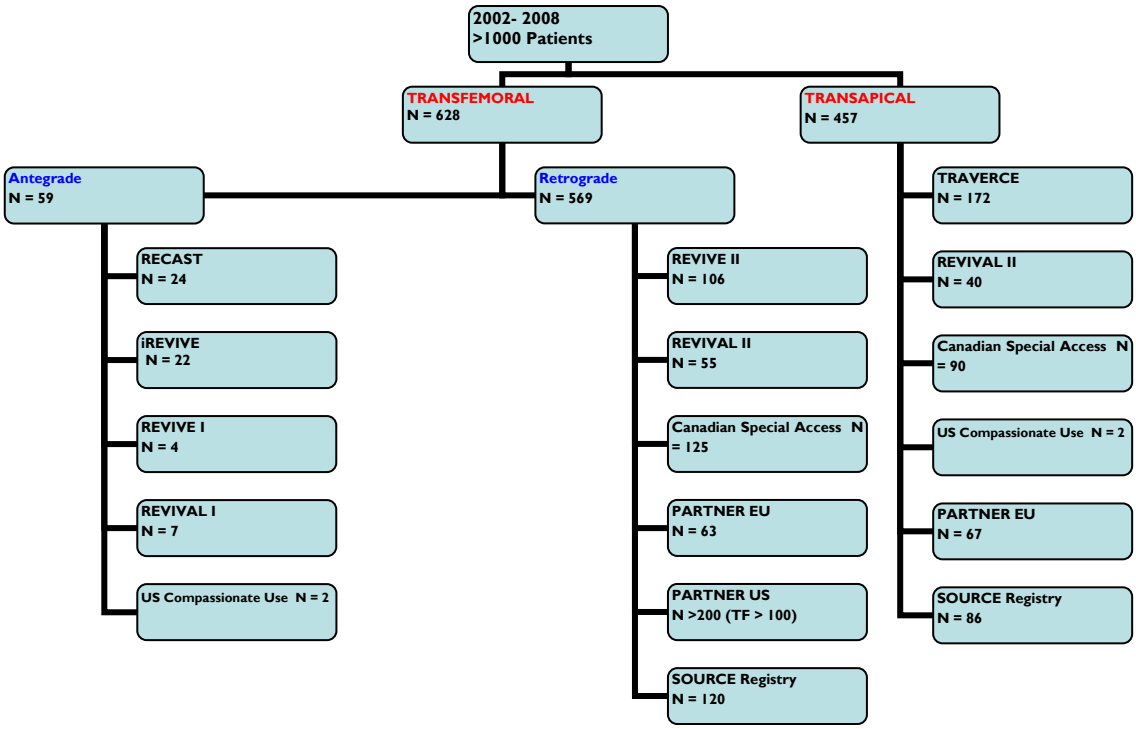
## CLASSIFICATION OF ECONOMIC STUDIES

**Figure 8.2: Classification of economic studies**

| | | **Are both costs (inputs) and consequences (outputs) of the alternatives examined?** | | |
|---|---|---|---|---|
| | | **No** | | **Yes** |
| | | Examines consequences only | Examines costs only | |
| **Is there a comparison of at least two alternatives?** | **No** | Partial evaluation | | Partial evaluation |
| | | Outcome description | Cost description | Cost-outcome description |
| | **Yes** | Partial evaluation | | Full economic evaluation |
| | | Efficacy or effectiveness evaluation | Cost comparison | Cost-minimisation analysis (CMA)<br>Cost-effectiveness analysis (CEA)<br>Cost-utility analysis (CUA)<br>Cost-benefit analysis (CBA) |

# APPENDIX 3

**Figure 8.3. Worldwide Experience with the Edwards SAPIEN™ PAV, as reported by Edwards Lifesciences, May 2008.**




Data resulting from these registries have at most been partially published in peer reviewed journals. "Antegrade" refers to the initial patient series and are referred to in the text as "the Rouen experience".

REVIVAL II: peRcutaneous EndoVascular Implantation of VALves: feasibility investigation, conducted in the US. Registry contains both a transfemoral and a transapical arm.

REVIVE II: feasibility investigation, conducted in Europe. Transarterial approach. 26 mm device.

PARTNER (Placement of AoRTic TraNscathetER Valve Trial) EU was the European feasibility register conducted after the study sponsor, Edwards Lifesciences, had filed for CE Mark approval in Europe but had not yet been granted marketing clearance.

SOURCE, Edward's postmarketing registry.

The TRAVERCE feasibility study, assessed the European experience with transapical aortic valve replacement from December 2004 to April 2008.

The PARTNER (Placement of AoRTic TraNscathetER Valve Trial) trial, sometimes referred to as the "PARTNER US" or the "PARTNER IDE" trial is a randomised, open label trial (cfr text for details). To avoid ambiguity with the homonymic European observational study, the United States based RCT often is referred to as the "PARTNER US" or the "PARTNER IDE" trial.

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