



Australian Government
Department of Health and Ageing



Horizon Scanning Technology
Prioritising Summary
Percutaneous aortic valve replacement

February 2007
(Updated August 2007)



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



**Royal Australasian
College of Surgeons**

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Enquiries about the content of the report should be directed to:

HealthPACT Secretariat
Department of Health and Ageing
MDP 106
GPO Box 9848
Canberra ACT 2606
AUSTRALIA

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

This Horizon scanning prioritising summary was prepared by Mr. Luis Zamora from the Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S).

PRIORITISING SUMMARY

REGISTER ID: S000021 REFERRAL FROM HEALTHPACT

NAME OF TECHNOLOGY: PERCUTANEOUS AORTIC VALVE REPLACEMENT

PURPOSE AND TARGET GROUP: PERCUTANEOUS IMPLANTATION OF A BIOPROSTHETIC VALVE IN HIGH-RISK PATIENTS WITH AORTIC VALVE DISEASE, WITHOUT EXPOSING THEM TO RISKS ASSOCIATED WITH CARDIOPULMONARY BYPASS AND SURGERY

STAGE OF DEVELOPMENT (IN AUSTRALIA):

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

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

- | | | |
|---|-------------|-----|
| <input type="checkbox"/> Yes | ARTG number | N/A |
| <input checked="" type="checkbox"/> No | | |
| <input type="checkbox"/> Not applicable | | |

INTERNATIONAL UTILISATION:

COUNTRY	LEVEL OF USE		
	Trials Underway or Completed	Limited Use	Widely Diffused
Canada	✓		
France	✓		
Germany	✓		

IMPACT SUMMARY:

Edwards Lifesciences (California, United States) provides the Cribier-Edwards Aortic Percutaneous Heart Valve with the aim of providing haemodynamic improvement in patients who are too ill to undergo conventional cardiac valve repair surgery. The technology is currently not available in Australia or New Zealand, but if approved it would be available through a cardiovascular surgeon for patients with vulvular heart disease.

BACKGROUND

The heart is composed of four chambers, two small, round, upper chambers (atria) and two larger cone-shaped chambers (ventricles). The flow of blood through these four chambers is regulated by 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 (opening from the right atrium) and the outlet valve is called the pulmonary valve (opening to the pulmonary arteries). The inlet valve of the left ventricle is called the mitral valve (opening from the left

atrium) and the outlet valve is called the aortic valve (opening to the aorta). Each one of these one-way valves is made up of flaps (also called cusps or leaflets), which open and close to serve as one-way gates for blood flow.

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 (causing regurgitation), or insufficient opening of the valve (causing reduced blood flow and creating stenosis) are two disorders which can affect any of the heart's valves (Boon and Bloomfield 2002). Sometimes both disorders can affect one valve at the same time.

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 ventricle contraction), the aortic valve opens and allows blood to flow from the left ventricle to the aorta (Nishimura 2002). During diastole (the period of left ventricle relaxation) the aortic valve completely closes, preventing the flow of blood into the aorta as blood fills the left ventricle from the lungs through the left atrium across the mitral valve, in preparation for the next contraction (Nishimura 2002).

During 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. This increases the volume of blood in the left ventricle, which increases the pressure of the blood in the left ventricle and in turn increases the amount of work the heart has to do. As a result, hypertrophy of the ventricular muscular walls and dilation of the chambers of the ventricles occurs to compensate for the increased volume of blood (Nishimura 2002). Despite this however, the heart may still be unable to pump blood adequately and heart failure may develop.

In patients who have 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 results in thickening of the left ventricle wall as the ventricle must work harder to pump blood through the narrowed valve. As the heart muscle thickens, increased blood supply from the coronary arteries is required. Eventually the supply becomes inadequate and heart failure can develop. In some cases if the stenosis is severe, sudden death may occur (Nishimura 2002).

CLINICAL NEED AND BURDEN OF DISEASE

Aortic regurgitation and aortic stenosis can result from similar structural abnormalities of the valve, such as being born with a valve consisting of two cusps instead of three.

Aortic regurgitation can result from enlargement of the aorta, which stretches the cusps of the valve. Infection of the aortic valve (infective endocarditis), or a tear in the aorta can cause acute onset of aortic regurgitation (Nishimura 2002). Common symptoms of aortic regurgitation include shortness of breath or chest discomfort; however patients with chronic aortic regurgitation may be asymptomatic for decades before any symptoms develop. Unless aortic regurgitation is mild, surgical replacement of the native aortic valve with an artificial valve is required. However, even when a patient is asymptomatic, surgery may still be required to prevent irreversible damage to heart muscle (Nishimura 2002).

Aortic stenosis can result from a progressive build-up of calcium and scar tissue on an abnormal congenital valve or from damage following rheumatic fever. The most common cause however, is due to calcium build-up on valve cusps that occurs with age (senile degenerative stenosis) (Nishimura 2002). Aortic stenosis can be asymptomatic (mild) or symptomatic (severe). Common symptoms include dyspnoea, angina and near-syncope. As with aortic regurgitation, surgical replacement of the native aortic valve with an artificial valve is required to prevent irreversible damage to the left ventricle.

Despite surgical intervention being a suitable treatment option for aortic stenosis and aortic regurgitation, there are increasing numbers of patients considered poor surgical candidates due to advanced age, co-morbidities and previous cardiac surgery (Munt and Webb 2006). Until recently, the only active treatment other than surgery that has been available to aortic stenosis patients has been balloon aortic valvuloplasty (Davidson et al. 2006). However, this option is not widely used, is normally offered as a last resort for the palliation of symptoms and does not provide sustained relief of symptoms (Cribier et al. 2006).

It has been estimated that between two and three percent of the elderly population in the United States have calcific aortic stenosis, while one to two percent of Americans have congenital bicuspid aortic valve disease (Davidson et al. 2006). In western populations (such as Australia and New Zealand) it has been reported that aortic stenosis is mostly degenerative, and usually presents in elderly patients with multiple co-morbidities, making them poor surgical candidates (Grube et al. 2006). The prevalence of aortic regurgitation and stenosis in Australia was not revealed in the searches conducted.

The Euro Heart Survey on valvular disease revealed that 33% of patients in New York Heart Association (NYHA) class III or IV with a single diseased valve were denied surgery because of co-morbidities and a short life expectancy (Euro Heart Survey 2006). Hence a percutaneous approach in which patients are not exposed to the risks of surgery has potentially large implications for these patients.

Currently there are two percutaneous heart valves available for investigational purposes. The Cribier-Edwards PHV (Edwards Lifesciences, Irvine, California, United States) is a bioprosthetic valve mounted on a balloon catheter and device for crimping the balloon onto a delivery catheter. The PHV is composed of a stainless steel balloon expandable stent with an integrated unidirectional tri-leaflet valve made of equine pericardium (Cribier et al 2006). The PHV can be implanted either via an antegrade femoral venous transeptal approach or retrograde femoral artery approach (Cribier et al. 2006). The second PHV is the CoreValve (CoreValve, Irvine, California, United States). In contrast to the Cribier-Edwards PHV, the CoreValve is a self expanding aortic valve prosthesis intended for retrograde delivery across the aortic valve (Grube et al 2006).

DIFFUSION

Percutaneous aortic valve replacement is not currently practiced in Australia.

COMPARATORS

Surgical repair or replacement of the native diseased aortic valve with a prosthetic valve is currently the best treatment option for aortic stenosis and aortic regurgitation (Munt and Webb 2006). For patients with aortic stenosis, aortic balloon valvuloplasty may also provide symptom relief, although it does not provide sustained improvements (Nishimura 2002).

SAFETY AND EFFECTIVENESS ISSUES

The first human study of the Cribier-Edwards PHV was reported by the developers of the valve in 2002 (Cribier et al. 2002). Since that time Cribier and colleagues have performed implantation of the device in six patients in the Initial Registry of Endo Vascular Implantation of Valves in Europe (I-REVIVE) trial (Cribier et al. 2004). This was followed in 2006 by the publication of mid-term results of 36 patients (including two of the six involved in I-

REVIVE) in the Registry of Endovascular Critical Aortic Stenosis Treatment (RECAST) trial (Cribier et al. 2006).

Cribier et al. (2004) reported on the implantation of the PHV (Percutaneous Valve Technologies Inc., Fort Lee, New Jersey, United States) in six (five male and one female) patients aged 75 ± 12 years, suffering severe aortic stenosis and multiple co-morbidities who were unsuitable for surgery. In addition to aortic stenosis, four patients also suffered from moderate to severe aortic regurgitation while mitral regurgitation was present in five patients. Prior to implantation of the PHV, three patients were in cardiogenic shock and all were classified as NYHA class IV (severe limitations and experience of symptoms at rest). Furthermore, at baseline these patients had a mean aortic valve area (AVA; measured by continuity equation) of $\leq 0.6 \text{ cm}^2$, while a low transvalvular gradient ($< 50 \text{ mm Hg}$) was present in all but one patient. Implantation of the PHV was performed via the antegrade trans-septal approach (i.e. femoral transvenous procedure with antegrade access to the aortic valve) and took a mean of 134 ± 23 minutes to perform.

Successful and accurate delivery of the PHV was achieved in five of six patients. The patient in whom successful delivery was not achieved was in cardiogenic shock, and had severe aortic stenosis associated with massive aortic regurgitation as a result of a previous aortic balloon valvuloplasty-induced tear. The patient died following ejection of the balloon-PHV assembly in the aorta at the time of full balloon inflation. It was revealed that in this patient the valve leaflets were disconnected from the annulus on one-third of its circumference, however it was not specified if this was a direct consequence of the PHV implantation procedure. In all other patients the PHV was strongly anchored within the native valve. Two patients (including the previously mentioned deceased patient) suffered from hemodynamic collapse following balloon pre-dilation requiring transient external cardiac massage and adrenalin infusion. At weeks two, four and 18, three patients died from non-cardiac complications. At the eight week follow-up period, the last two patients to receive the PHV were stable and showed no signs of heart failure.

After PHV implantation, supra-aortic angiography revealed mild or severe aortic regurgitation in three and two cases respectively, as well as patent coronary arteries. Echocardiographic data was available for five patients in whom PHV implantation was achieved. Mean gradient and AVA recordings were obtained pre- and post-implantation as well as at a follow-up period (two weeks for one patient and four weeks for the remaining five patients). Aortic regurgitation grades and ejection fractions were recorded pre- and post-implantation. All patients experienced improvements in mean gradient and AVA post-implantation and at follow-up. The mean gradient improved from $38 \pm 11 \text{ mm Hg}$ at pre-implantation to $5.6 \pm 3.4 \text{ mm Hg}$ post-implantation and rose slightly to $7.4 \pm 3.4 \text{ mm Hg}$ at follow-up (both $p = 0.04$ compared to baseline). The AVA improved from $0.49 \pm 0.08 \text{ cm}^2$ pre-implantation to $1.66 \pm 0.13 \text{ cm}^2$ post-implantation and $1.63 \pm 0.05 \text{ cm}^2$ at follow-up (both $p = 0.04$ compared to baseline). The mean ejection fraction (EF) also improved in all patients, with the mean value increasing from $24 \pm 9.5\%$ at baseline to $41 \pm 12\%$ at follow-up ($p < 0.04$). However, it must be noted that very few patients were included in the study and hence differences observed must be viewed with caution. Following implantation, aortic regurgitation was seen in all patients and as suggested by the authors, may have been caused by imperfect apposition of the PHV stent frame against the diseased native valvular structures at the site of calcific nodules. Echocardiographic assessment confirmed normal PHV function during follow-up, as well as no substantial change in the transvascular gradient, AVA or aortic regurgitation from the post-implantation period. Although the shape of the frame was maintained over time, colour flow Doppler studies revealed mild transatrial shunting in all patients (Cribier et al. 2004).

The 2000 study by Cribier and colleagues reported on patients recruited for PHV implantation including two from the previously reported Cribier et al. (2004), patients enrolled in the I-REVIVE trial (not published) and patients enrolled in the RECAST trial (a continuation of I-REVIVE with minor protocol changes resulting from the acquisition of Percutaneous Valve

Technologies Inc. by Edwards Lifesciences) (Cribier et al. 2006). In this report, 36 patients (mean age 80 ± 7 years) with severe aortic stenosis ($\leq 0.7 \text{ cm}^2$) and ≥ 3 co-morbid conditions, not considered surgical candidates by cardiac surgeons were recruited to receive the Cribier-Edwards PHV. Both the antegrade trans-septal and the retrograde approach were used to deliver the Cribier-Edwards PHV. The mean procedural time for antegrade implantation was 164 ± 38 minutes in patients in the I-REVIVE trial and 130 ± 30 minutes in patients enrolled in the RECAST trial. Though 36 patients were recruited to receive PHV implantation, only 35 proceeded to the catheterisation laboratory as a result of one death prior to the procedure. One patient in cardiogenic shock arrested during pre-dilation of the aortic valve and subsequently died despite resuscitation attempts. There was a procedure cancellation in one patient following pre-dilation after it was revealed the annulus size was too large for the PHV. Therefore implantation was attempted in 33 patients (26 via antegrade and 7 via retrograde approach). In this report, procedural success was defined as accurate PHV placement in a sub-coronary position, improvement in hemodynamic parameters ($\geq 30\%$ reduction in mean transvalvular aortic gradient) and the absence of severe (grade 4) aortic regurgitation.

Twenty-two out of 26 antegrade attempts were successful. Four attempts had technical failures. Two patients could not hemodynamically tolerate the guidewire across the mitral valve and the procedure was aborted before PHV implantation. In another two the PHV migrated immediately after implantation, once due to the PHV being positioned too high and once because the native valve was mildly calcified with a large annulus. In both instances the PHV was deployed in the aorta without sequelae. In all four cases patients were discharged from the catheterisation laboratory in stable condition. Four of seven retrograde attempts were successful. In one, the stent-mounted catheter was too short to reach the aortic valve, and prevented implantation. In two, extensive calcification prevented retrograde crossing with the delivery system. In these patients the PHV was implanted in the descending aorta without sequelae. One patient received implantation via the antegrade approach. No atrial shunt was detected by oximetry at the end of the procedures. Twenty six patients were successfully implanted.

Baseline AVA (by trans-thoracic echocardiography) in successfully implanted patients was $0.6 \pm 0.09 \text{ cm}^2$ and improved to $1.7 \pm 0.11 \text{ cm}^2$ 24 hours after the procedure ($p < 0.0001$, $n = 25$). Further recordings at one, three, six, 12 and 24 months suggest a sustained effect with recordings of $1.7 \pm 0.11 \text{ cm}^2$ ($n = 16$), $1.7 \pm 0.09 \text{ cm}^2$ ($n = 12$), $1.6 \pm 0.07 \text{ cm}^2$ ($n = 7$), $1.8 \pm 0.18 \text{ cm}^2$ ($n = 3$) and $1.64 \pm 0.04 \text{ cm}^2$ ($n = 2$), respectively. However, it must be noted that the numbers of patients available for recordings decreased substantially over time making accurate assessment of the effectiveness of the PHV difficult. At baseline the mean aortic gradient in the successfully implanted patients was $37 \pm 13 \text{ mm Hg}$. This figure reduced to $9 \pm 2 \text{ mm Hg}$ 24 hours after the procedure ($p < 0.0001$, $n = 25$). Stability of this effect was also suggested by the one, three, six, 12 and 24 month recordings of $10 \pm 2 \text{ mm Hg}$ ($n = 16$), $11 \pm 2 \text{ mm Hg}$ ($n = 12$), $11 \pm 2 \text{ mm Hg}$ ($n = 7$), $10 \pm 1 \text{ mm Hg}$ ($n = 3$) and $12 \pm 1 \text{ mm Hg}$ ($n = 2$) respectively. Similar to AVA data are weakened by the decrease in numbers of patients available for follow-up. Ejection fraction was also monitored. Prior to the procedure, EF was $45 \pm 15\%$. This figure significantly improved to $53 \pm 14\%$ one week after the procedure ($p = 0.02$, $n = 22$). Unfortunately EF recordings were not reported for any of the follow-up periods. Following implantation of the PHV, paravalvular aortic regurgitation was observed. In 25 patients aortic regurgitation was determined by post-procedure echocardiography, with regurgitation mild (grade 0 to 1) in 10 patients, moderate (grade 2) in 10 patients and moderate to severe in 5 patients (grade 3). In the other two patients aortic regurgitation was determined by angiography (both grade 2). During follow-up paravalvular leakage remained unchanged in most patients. Two patients saw improvements of one grade at after three months. A further two saw improvements of one grade at after one week (Cribier et al. 2006).

During the procedure, six of 27 patients (22 successful antegrade, four successful retrograde and one successful conversion to antegrade) had complications. Two deaths were attributed to

cardiac tamponade. One patient had severe dextrorotation of the heart and suffered a trans-septal puncture. The second, was receiving chronic steroid therapy for pulmonary fibrosis and suffered a slow bleeding perforation of the right ventricle from the pacing lead, leading to infection and sepsis, after surgical repair. Another patient on chronic steroids for treatment of rheumatologic disease developed urosepsis three days after the procedure and died two days later. Another patient suffered complete heart block with temporary loss of pacing lead resulting in irreversible brain damage due to prolonged resuscitation, despite successful PHV implantation. One patient undergoing retrograde catheterization of the aortic valve developed a stroke followed by multi-organ failure and death at 33 days. Another death of unknown aetiology was reported in one patient who suffered intractable hypotension after removal of the 24F sheath from the femoral artery. In this patient the PHV was appropriately positioned and appeared normal. The remaining 21 patients were complication-free (Cribier et al. 2006).

At baseline, patients were NYHA class IV. After PHV implantation, five improved to NYHA class I, 14 to NYHA class II and 2 to NYHA class III (limited by severe lung disease). One patient died at 18 days as a result of ventricular arrhythmia. At two months a further three died of progressive renal failure. Three more patients died from a non-cardiac cause and another died from third degree heart block at three months (due to pace maker implantation complicated by pulmonary embolus and sepsis). Pneumonia caused another death at three months. Morphine overdose in a patient with metastatic breast cancer caused another death at 3.5 months; however there were no device related complications. At the time of writing, 11 patients were alive (three from I-REVIVE and eight from RECAST). The patients have returned to normal life and are only limited by previous conditions. Four are NYHA class I, six are NYHA class II and one patient is NYHA class III. Follow-up for these patients was as follows: nine months (n=2), 10 months (n=3), 11 months (n=1), 12 months (n=2), 23 months (n=1) and 26 months (n=2). While valve area of $1.69 \pm 0.10 \text{ cm}^2$, measured 3-24 months following PHV implantation remained unchanged, this provides little information regarding long term effectiveness of the PHV due to few patients available (Cribier et al. 2006).

Bauer et al. (2004) conducted another small study of PHV implantation in eight (six women and two men) severe aortic stenosis patients (mean age 82.6 ± 3.3 years) to evaluate the immediate short term effects of PHV implantation. In this study, tissue Doppler imaging was used to detect improvements in global and regional LV systolic function. Patients had an AVA of $< 0.7 \text{ cm}^2$ at baseline, suffered symptoms despite medical therapy (two in cardiogenic shock and all NYHA class IV) and had been previously denied surgical treatment due to haemodynamic instability and severe co-morbidities. As in the previous study, both the antegrade trans-septal approach and the retrograde arterial approach were utilised (six antegrade and two retrograde). When determined by echocardiography, baseline AVA was $0.59 \pm 0.11 \text{ cm}^2$, the peak pressure gradient was $78 \pm 19 \text{ mm Hg}$, the mean pressure gradient was $46 \pm 15 \text{ mm Hg}$ and the mean LVEF was $48 \pm 18\%$.

Replacement of the aortic valve was successful in all cases. The duration of the procedure was not stated. Following implantation of the PHV (24 hours) the mean pressure gradient improved to $8 \pm 3 \text{ mm Hg}$ ($p < 0.0001$) and the peak pressure gradient reduced to $20 \pm 7 \text{ mm Hg}$ ($p < 0.01$). Similarly, the AVA improved to $1.69 \pm 0.11 \text{ cm}^2$ ($p < 0.0001$), and both LV end-systolic pressure and LV end-diastolic pressure improved significantly at 24 hours from $165 \pm 27 \text{ mm Hg}$ to $131 \pm 30 \text{ mm Hg}$ ($p < 0.05$) and from $9 \pm 5 \text{ mm Hg}$ to $7 \pm 4 \text{ mm Hg}$ respectively. In terms of global and regional systolic function, both the LV end-diastolic volume and LV end-systolic volume were unchanged. However, the LV ejection fraction significantly improved from $48 \pm 18\%$ to $57 \pm 12\%$ ($p < 0.01$). Peak systolic tissue velocity in the LV posterior wall significantly improved from $2.2 \pm 0.5 \text{ cm/s}$ to $4.4 \pm 1.0 \text{ cm/s}$ ($p = 0.0003$) but did not improve in the anterior wall ($p = 0.29$). Peak systolic strain rate imaging at the anterior and posterior walls were significantly enhanced ($p = 0.002$ and $p = 0.009$ respectively). Similarly, the peak systolic strain at the anterior and posterior walls significantly improved ($p = 0.02$ for both) (Bauer et al. 2004). Although promising in the

immediate short term, this early study of PHV implantation does not provide the detail required to determine the long term safety or efficacy effects of the PHV. However, it can be concluded that PHV implantation in patients with severe symptomatic aortic stenosis has the potential to provide immediate improvement to patients as evidenced by AVA, pressure gradient improvements and global/regional systolic function indicators.

A recent paper by Webb and colleagues published earlier this year investigated the implantation of the Cribier-Edwards PHV in 18 patients (age 81 ± 6 years) with severe aortic stenosis and multiple co-morbidities without a reasonable surgical option. During the procedure, the first two patients experienced iliac artery complications. In one patient a short sheath was used for access to internal iliac artery. During passage of prosthesis through the atherosclerotic artery, a localised dissection resulted in iliac occlusion requiring surgical repair. The second patient had recently undergone repeat thoracotomy (in addition to prior coronary bypass surgery) during which aortic valve replacement was aborted due to an unsuspected porcelain aorta. Following uneventful implantation of the PHV this patient suffered a sudden haemorrhage from the iliac artery as a result of surgical removal of the 22F sheath which was advanced through a heavily calcified common iliac artery. The artery was surgically repaired; however multi-system failure two weeks later resulted in death. Ventricular fibrillation was reported in two cases, minor stroke and transient heart block was reported in one patient and transfusion of ≥ 2 U was reported in another five cases. No further complications were reported. At the 30 day follow-up, two deaths were reported. One death was a result of iliac perforation (described above). The second death, according to the authors, was likely due to left coronary obstruction by a displaced native aortic valve leaflet excrescence. At 73 ± 49 days follow-up, 16 patients were alive. In two patients, prosthetic valve embolisation occurred immediately after deflation of the deployment balloon. Both received the smaller PHV. PHV positioning was successful in all but one case where the PHV could not cross the stenotic calcified valve. In this case the PHV was successfully removed. In no patient did the stent appear to extend above the ostium of the coronary arteries. In one patient the stent remained below the coronary ostia (patient had pre-procedural cardiogenic shock), however an unusually bulky calcified native leaflet was displaced over the left coronary ostium. In this patient, initial improvement was followed by deterioration due to pneumonia and eventual withdrawal of active treatment five days later. Post-mortem showed a calcified valvular nodule obstructing the left main coronary artery. In this study, seven patients received the larger (26 mm diameter) PHV while eight received the smaller (23 mm diameter) PHV. Both sets of patients had similar echocardiographically determined native valve areas (0.7 ± 0.2 versus 0.6 ± 0.1 cm²) but patients with a larger stent had a slightly larger annulus diameter (23.7 ± 1.5 versus 22.0 ± 1.4 mm). Post-procedurally, valve area with the larger PHV was greater (1.6 ± 0.2 versus 1.3 ± 0.5 cm²), paravalvular regurgitation was less (median 1+ versus 2+/4) and valve embolisation did not occur (0 versus 2) (Webb et al. 2006).

Grube and colleagues investigated the effects of the CoreValve, a self expanding PHV able to conform to the dimensions of a person's aorta and aortic valve (Grube et al. 2006). The authors implanted the CoreValve using the retrograde approach, in 25 patients (20 women and five men) aged 80.3 ± 5.4 years, all of whom had aortic stenosis and/or aortic regurgitation. The patients included had native aortic valve stenosis with an aortic area of less than 1 cm² and/or aortic valve regurgitation of $\geq 3+$, aortic valve annulus diameter between 20 mm and 23 mm, diameter of the ascending aorta three centimetres above the annulus of ≤ 30 mm, as well as concomitant co-morbidities. All patients were unsuitable for surgery determined by a cardiologist and cardiovascular surgeon. The first ten patients received the first generation device (composed of bovine pericardial tissue constrained within a 24F delivery sheath) while the remaining patients received the second generation device (composed of porcine pericardial tissue within a 21F delivery sheath). At baseline, patients had peak transvascular aortic pressure gradient of 69.3 ± 13.9 mm Hg and a mean aortic valve area 0.72 ± 0.13 cm², while 96% of patients were classified NYHA class III or IV. Successful, stable device placement and function (assessed by angiography and echocardiography) was achieved in 22

patients. Two patients (one with the new and one with old prosthesis) experienced significant paravalvular leakage because the prosthesis was not deployed deep enough within the native valve (prosthesis not completely anchored in native valve area), however the upper part of the prosthesis (positioned in the ascending aorta) provided stable fixation of the device without migration or embolisation. However, these patients required urgent open heart surgery to remove the device and replace it with conventional mechanical valve prosthesis. In one patient the device could not cross the heavily calcified native valve despite successful pre-dilatation. This patient was deemed inoperable and received balloon valvuloplasty only. The patient died 12 hours later from acute heart failure. Another patient died on the second post procedural day despite successful implantation due to delayed pericardial tamponade secondary to small, initially asymptomatic wire perforation of the left ventricle. Three more patients died on post procedural days nine, 13 and 15 from progressive hemodynamic failure despite intact valve function (n = 1), disseminated intravascular coagulation (n = 1), and non cardiac sepsis with multi-organ failure (n = 1) (Grube et al. 2006).

Therefore, 21 out of 25 patients had acute procedural success (i.e. device success with no peri-procedural major adverse cardiovascular and cerebral events; MACCE) during the first 48 hours after implantation. MACCEs included death, major arrhythmia, myocardial infarction, cardiac tamponade, stroke, urgent/emergent conversion to surgery or balloon valvuloplasty, emergent percutaneous coronary intervention, cardiogenic shock, endocarditis or aortic dissection. Overall, there were eight in-hospital MACCEs (five deaths, one cardiac tamponade, one stroke and two conversions to surgery). Major bleeding occurred in six patients (five with the first generation device and one with the second generation device). Peak pressure gradient reduced from 69.90 ± 22.96 mm Hg to 21.31 ± 5.05 mm Hg (after implantation) to 22.10 ± 3.61 mm Hg (30 day follow-up). Mean pressure gradient also reduced from 44.24 ± 10.79 mm Hg to 12.38 ± 3.03 mm Hg (after implantation) to 11.82 ± 3.42 mm Hg (30 days). Aortic regurgitation also improved. At baseline, four patients were grade 2+, 10 were 1+ and seven were grade 0. After CoreValve implantation this improved slightly to four patients in grade 2+, seven in grade 1+ and ten in grade 0. At the 30 day follow-up, out of 18 available patients, one was grade 2+, eight were grade 1+ and nine were grade 0. There were no reports of valve migration or thrombosis. Additionally, no patient developed myocardial ischemia. All patients developed thrombocytopenia between days one and six, although this was expected due to the use of extracorporeal circulation. The prescription of clopidogrel was performed in three phases. In phase I (patients one to three), a 300 mg loading dose of clopidogrel was given prior to the procedure. In two of these major bleeding occurred and the loading dose of clopidogrel was suspended in patient's four to seven (phase 2). After phase 2 patients developed persistent thrombocytopenia, the clopidogrel load was reinstated in phase 3 (patients eight to 25). Patients were treated with 25 mg per day indefinitely. Two patients in phase 1 with procedural success had transient and mild thrombocytopenia. In the three patients with procedural success in phase 2, post procedure thrombocytopenia was severe and prolonged, and a fatal disseminated intravascular coagulation developed in one. In the phase three patients, post procedure thrombocytopenia was again mild and transient in all but 1 of the 18 patients with procedural success. None of the 18 patients in whom the device was successfully implanted and who survived to discharge had an adverse event within the 30 day follow-up after leaving hospital (Grube et al. 2006).

Of the 18 patients who survived to discharge (with device success) there were no adverse events to 30 days follow-up, valve function was stable and clinical status improved from NYHA class III (n=17) and II (n=1) to class II (n=12) or I (n=6) at the 30 days. The 180 and 365 day follow-up results were available in seven and two patients respectively. Left ventricular failure (without valve deterioration) led to one patient being re-hospitalised while the other eight patients were alive and clinically unchanged, with stable valve function. Only one patient developed severe (3+ or 4+) aortic regurgitation after CoreValve replacement. Device configurations of the CoreValve used in this study limited the use of the device to

patients with a relatively small valve annulus and a narrow ascending aorta. Therefore the majority of patients who qualified for this study were women (Grube et al. 2006).

2007 six month update

A search of relevant databases, online journals and the Internet was conducted in June 2007, following the recommendation in February 2007 that percutaneous aortic valve replacement be monitored for six months. A total of three studies on the safety and effectiveness of this procedure were identified. All three studies described the use of the Cribier-Edwards valve (case series studies). An additional case report study on the CoreValve in an elderly patient was identified but not included in the present update.

Walther and colleagues reported on the implantation of the Cribier-Edwards percutaneous heart valve on 30 patients (82 ± 5.1 years) with severe symptomatic aortic stenosis (aortic valve area $< 0.9 \text{ cm}^2$) using an antegrade trans-apical approach (Walther et al. 2007). All patients included in the study had an aortic annulus of ≤ 24 mm and equally distributed calcification. A wide variety of comorbidities were present in this cohort of patients, some of which were reflected as a risk of mortality of $> 11\%$ based on the logistic EuroSCORE.

Implantation of either the 23 mm ($n = 8$) or 26 mm ($n = 22$) Cribier-Edwards prosthesis was performed via a small anterolateral minithoracotomy with or without femoral extracorporeal circulation in 13 and 17 patients respectively. The procedure was successful in all but one patient who had severe eccentric calcification of one of the native aortic valve cusps. The patient required early conversion to full sternotomy and conventional valve replacement.

Perioperative laboratory examinations revealed a lack of increase in myocardial enzymes despite apical puncture and the application of apical purse-string sutures. The cardiac rhythm of patients did not appear to be affected by implantation of the Cribier-Edwards prosthesis. Prior to implantation, 18 patients were in sinus rhythm, 10 in atrial fibrillation and two required a pacemaker. Postoperatively, this changed to 17 patients in sinus rhythm, nine in atrial fibrillation and four required a pacemaker.

Seven patients went on to have a completely uneventful postoperative period. Three patients died in hospital, all due to non valvular causes (acute abdomen followed by multiorgan failure on postoperative day 18 and 86, and severe biventricular myocardial failure during induction of anaesthesia leading to death on postoperative day 3). In all three cases an autopsy confirmed correct valve positioning and patent coronary arteries. A range of other in hospital morbidities were reported and are shown in Table 1.

Table 1. Morbidities reported during the in-hospital period.

Morbidity	Number of patients
Pleural effusion	7
Supraventricular tachyarrhythmia	9
Transient hemofiltration	4
Tracheostomy for weaning off ventilation	3
Cardiopulmonary resuscitation	2
Pericardial effusion (medical therapy)	2
Other	14

The 29 patients who underwent implantation of the Cribier-Edwards prosthesis underwent echocardiographic analysis at the early postoperative (pre-discharge) period.

In terms of haemodynamic function, all patients experienced complete instantaneous relief of aortic stenosis following valve placement. Although statistical analysis was not performed, early postoperative results demonstrated an improvement in the maximum transvalvular blood flow velocity, maximum transvalvular pressure gradient, mean transvalvular pressure gradient, left ventricular posterior wall end diastolic diameter and ejection fraction. During the early postoperative period, aortic regurgitation was observed in 14 patients (transvalvular in five and paravalvular in nine). Three patients experienced only a trace of aortic regurgitation, nine experienced minimal and the remaining two experienced moderate regurgitation.

Following discharge one patient (with porcelain aorta) required re-operation on postoperative day 37 as a result of new onset severe aortic valve regurgitation. As of October 2006, patients had been followed up for 127 ± 63 days and patients were scheduled to undergo further follow-ups at six months, one year, and annually thereafter.

Ye et al. (2007) reported their experience implanting the Cribier-Edwards valve using a transapical approach via minithoracotomy in seven symptomatic aortic stenosis patients (77 ± 10 years) not suitable for surgical aortic valve replacement or transfemoral percutaneous heart valve implantation due to significant comorbidities. Patients had a mortality risk based on the logistic Euroscore of $31 \pm 23\%$.

The 26 mm diameter Cribier-Edwards prosthesis was successfully implanted in all seven patients. Intraoperatively, two patients experienced moderate paravalvular regurgitation however re-dilation expanded the prosthesis further and reduced paravalvular regurgitation satisfactorily. No complications or deaths were reported.

Five of the seven patients were discharged following implantation of the prosthesis. Of the remaining two, one patient was transferred to another hospital for convalescent care and the other died on postoperative day 12 from pneumonia. Prior to discharge or transfer the median hospital stay was 8 days, due to the preoperative comorbidities of the patients.

Postoperatively there was one case of pleural effusion and one case of urinary tract infection reported. Follow-ups at one and six months demonstrated either complete resolution or significant improvement of preoperative symptoms related to aortic stenosis. One patient with preoperative end stage lung disease died on postoperative day 51 from the disease. Another death attributed to cancer was reported on postoperative day 85. Echocardiographic studies prior to discharge showed well seated aortic valves with normal valve function in all seven patients.

While no statistical tests were performed due to small sample size, the aortic valve area, aortic mean gradient, and ejection fraction, all improved immediately after the procedure and either maintained or increased their improvement at one and six months. Similarly the median aortic regurgitation grades also improved over the six months from baseline (Ye et al. 2007).

The third study, reported the use of the Cribier-Edwards prosthesis in 19 patients with severe aortic stenosis, however was only available as an abstract (Simon et al. 2007). In this study, valve positioning was successful in 16 patients while the remaining three patients were converted to conventional aortic valve replacement. Cardiopulmonary bypass was required in the initial seven patients (in four patients to treat bleeding complications).

Three deaths were reported during the 30 day period, with one being attributed to the valve prosthesis. Bleeding (diffuse in three, related to apical access in one, intercostals in one and lung laceration in one) was reported in six patients and necessitated operative revision. Favourable results were also reported in terms of aortic insufficiency and aortic gradients (Simon et al. 2007).

2007 HealthPACT action:

The new studies published on percutaneous aortic valve replacement are limited by small number of participants and short follow-up periods. The retrieved studies utilised the Cribier-Edwards percutaneous valve and found immediate improvements post-implantation, however no statistical tests were performed due to the small patient cohort. Meanwhile, no new studies reporting the use of the CoreValve were published during the 6 month monitor period. Percutaneous aortic valve replacement will be monitored for a further 12 months to retrieve additional safety and efficacy evidence considering the potential uptake of this procedure within the healthcare system.

Number of studies included

Total number of studies 3
Level IV intervention evidence 3

References

Simon P, Kasimir MT, Glogar D, Baumgartner H, Base E, Koinig H, Wolner E. trans-apical valve replacement with the Cribier-Edwards prosthesis in high risk patients with severe aortic stenosis. *The Thoracic and Cardiovascular Surgeon* 2007. 55 (Suppl 1) [Abstract].

Walther T, Falk V, Borger MA, Dewey T, Wimmer-Greinecker G, Schuler G, Mack M, Mohr FW. Minimally invasive transapical beating heart aortic valve implantation – proof of concept. *European Journal of Cardio-thoracic Surgery* 2007. 31(1): 9-15.

Ye J, Cheung A, Lichtenstein SV, Pasupati S, Carere RG, Thompson CR, Sinhal A, Webb JG. Six-month outcome of transapical transcatheter aortic valve implantation in the initial seven patients. *European Journal of Cardio-thoracic Surgery* 2007. 31(1): 16-21.

COST IMPACT

The specific costs of percutaneous aortic valve replacement were not revealed in the searches conducted. In addition to the device itself, the implantation procedure may attract further costs. The Medicare Benefits Schedule reimbursement fees for procedures related to valve replacements are listed in Table 1:

Table 1 Medical Benefits Schedule of fees for procedures related to valve replacements (Medicare Australia 2006)

Category	Item Number	Benefit (AUD)	Number of Claims (July 2005 to June 2006)
Valve replacement with bioprosthesis or mechanical prosthesis.	38488	\$1687.40	1918
Valve replacement with allograft (subcoronary or cylindrical implant) or unstented xenograft.	38489	\$2006.80	80
Repair or replacement of the ascending thoracic aorta with aortic valve replacement or repair, and implantation of coronary arteries.	38556	\$2743.45	168
Repair or replacement of the aortic arch and ascending thoracic aorta, not involving valve replacement or repair or coronary artery implantation.	38559	\$2236.50	31
Repair or replacement of the aortic arch and ascending thoracic aorta, with aortic valve replacement or repair, without implantation of coronary arteries.	38562	\$2743.45	35
Repair or replacement of the aortic arch and ascending thoracic aorta, with aortic valve replacement or repair, and implantation of coronary arteries.	38565	\$3077.00	54

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

No issues were identified in the literature retrieved.

OTHER ISSUES

Currently, the Cribier-Edwards PHV and the CoreValve prosthesis are the only devices which have been trialled on humans. However, there are other devices in pre-clinical development including the Lotus self-expanding valve from Sadra Medical (Campbell, California, United States), the Aortx valve from Aortx Inc., the Bonhoeffer valve and the eNitinol thin membrane PercValve (Davidson et al. 2006).

HEALTHPACT ACTION:

Percutaneous aortic valve replacement appears to be a promising new alternative for patients who would otherwise have few options; however this procedure is still in its infancy. Balloon aortic valvuloplasty is frequently complicated by restenosis within 6 months to 1 year after the procedure (Babaliaros et al. 2006), therefore provided the valves that are developed can maintain long-term functionality without adverse events, percutaneous aortic valve replacement offers a potentially new form of treatment for these patients. However, despite the indications of safety and efficacy described in the studies presented, more studies with larger numbers of patients and longer follow-up periods are required to confirm this. Based on the limited evidence available, HealthPACT has recommended that the technology be monitored.

- | | |
|--|--|
| <input type="checkbox"/> Horizon Scanning Report | <input type="checkbox"/> Full Health Technology Assessment |
| <input checked="" type="checkbox"/> Monitor | <input type="checkbox"/> Archive |
| <input type="checkbox"/> Refer | <input type="checkbox"/> Decision pending |

SOURCES OF FURTHER INFORMATION:

Edwards Lifesciences. Last updated 2006.

<http://www.edwards.com/products/percutaneousvalves/> [Accessed November 2006].

Vahanian A, Acar C. Percutaneous valve procedures: what is the future? *Current Opinion in Cardiology* 2005; 20(2): 100-106.

LIST OF STUDIES INCLUDED

Total number of studies 4
 Level IV intervention evidence

SEARCH CRITERIA TO BE USED:

'Percutaneous aortic valve', 'Aortic valve', 'Aortic valve replacement', 'CoreValve', 'Cribier-Edwards', 'Percutaneous heart valve'

REFERENCES

Bauer F, Eltchaninoff H, Tron C, Lesault PF, Agatiello C, Nercolini D, Derumeaux G, Cribier A. Acute improvement in global and regional left ventricular systolic function after percutaneous heart valve implantation in patients with symptomatic aortic stenosis. *Circulation* 2004; 110(11): 1473-1476.

Boon NA, Bloomfield P. The medical management of valvar heart disease. *Heart* 2002; 87(4): 395-400.

Cribier A, Eltchaninoff H, Bash A, Borenstein N, Tron C, Bauer F, Derumeaux G, Anselme F, Laborde F, Leon MB. Percutaneous transcatheter implantation of an aortic valve prosthesis for calcific aortic stenosis: First human case description. *Circulation* 2002; 106(24): 3006-3008.

Cribier A, Eltchaninoff H, Tron C, Bauer F, Gerber L. Percutaneous implantation of aortic valve prosthesis in patient with calcific aortic stenosis. *Journal of Interventional Cardiology* 2006; 19(S5): S87-S96.

Cribier A, Eltchaninoff H, Tron C, Nauer F, Agatiello C, Sebah L, Bash A, Nusimovici D, Litzler PY, Bessou JP, Leon MB. Early experience with percutaneous transcatheter implantation of heart valve prosthesis for the treatment of end-stage inoperable patient with calcific aortic stenosis. *Journal of the American College of Cardiology* 2004; 43(4): 698-703.

Davidson MJ, White JK, Baim DS. Percutaneous therapies for valvular heart disease. *Cardiovascular Pathology* 2006; 15(3): 123-129.

Euro Heart Survey. Last updated 2006. <http://www.escardio.org/knowledge/ehs/> [Accessed November 2006].

Grube E, Laborde JC, Gerckens U, Felderhoff T, Sauren B, Buellesfeld L, Mueller R, Menichelli M, Schmidt T, Zickmann B, Iversen S, Stone GW. Percutaneous implantation of the CoreValve self-expanding valve prosthesis in high-risk patients with aortic valve disease: The Siegburg first-in-man study. *Circulation* 2006; 114(15): 1616-1624.

Medicare Australia: Medicare benefits Schedule. Last update 2006.
<http://www9.health.gov.au/mbs/> [Accessed December 2006].

Munt B, Webb J. Percutaneous valve repair and replacement techniques. *Heart* 2006; 92(10): 1369-1372.

Nishimura RA. Aortic valve disease. *Circulation* 2002; 106(7): 770-772.

Webb JG, Chandavimol M, Thompson CR, Ricci DR, Carere RG, Munt BI, Buller CE, Pasupati S, Lichtenstein S. Percutaneous aortic valve implantation retrograde from the femoral artery. *Circulation* 2006; 113(6): 842-850.