Bazian

FINAL REPORT

Percutaneous aortic valve replacement for severe aortic stenosis

Part A: Technology assessment and impact model for East Midlands Specialist Commissioning Group

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Section 1 – The Briefing

1.1 Policy background

Percutaneous aortic valve replacement (PAVR) procedures are increasingly being used as alternatives to open heart surgery for people with severe aortic stenosis. So far, the technology has been used for severely symptomatic adults who are unfit for conventional valve replacement through open heart surgery. East Midlands SCG has commissioned Bazian to conduct an independent, evidence-based analysis of the likely local clinical and cost impact of PAVR in the region. This is in response to requests for funding to provide these procedures and will contribute in part to formulation of local policy around the technology.

Aortic stenosis is common in the elderly and prevalence is increasing. In 2005-2006 there were 10,396 hospital diagnoses of aortic stenosis in England, the majority in people aged over 60 years. For those with severe symptomatic disease, the gold standard treatment is aortic valve replacement, which is a major surgical procedure.[1] However, about a third of people requiring surgery are not referred for this procedure because of the operative risks associated with advanced age and comorbidities.[2] Untreated, severe symptomatic aortic stenosis has a high mortality rate. Medical alternatives can be used to manage symptoms, but are not effective in the long term. PAVR procedures, which can be carried out in the cardiac catheter lab, are minimally invasive. They are therefore advocated by some as an attractive treatment option, both for people in whom open surgery is currently considered too risky, and as a potentially safer and more cost effective substitute to open surgery.

Percutaneous procedures are, however, not without associated risks to patients and costs to the healthcare system. The technique is relatively new (first human case in 2002) and is highly specialised. The consumables alone (prosthetic valve and delivery system) currently cost over £11,000. In addition, the patient group in which the procedure has so far been tried is older adults who are unsuitable for major surgery. Their survival and quality of life will be limited by their comorbidities.

To date, little is known about the comparative effectiveness of percutaneous valve replacement and medical treatment in those unfit for major surgery. Further evidence is also required on the effectiveness of the percutaneous therapy when compared to open heart aortic valve replacement for people who are fit for both.

1.2 The briefing questions

Against this policy background, Bazian conducted a broad literature search to review the evidence base for percutaneous aortic valve replacement (PAVR) technologies to address the following questions:

- What is the efficacy of percutaneous aortic valve implantation using either CoreValve or Edwards valves compared to other therapies in adults with aortic stenosis who are unsuitable for open heart surgery?
- What is the efficacy of percutaneous aortic valve implantation using either CoreValve or Edwards valves compared to open heart valve replacement in adults with aortic stenosis who are suitable for open surgery?
- What does the literature say regarding issues of likely cost effectiveness, patient prioritisation and future potential for this technology?

Key note:

In common usage, the term percutaneous aortic valve replacement (PAVR) is used to refer to both 1) the retrograde (transarterial) approach, and 2) the antegrade (transvenous) approach. The antegrade approach, however, is no longer favoured because of the risks incurred by the anatomical approach (crossing the interatrial septum). *Therefore, only studies that examined the retrograde approach or both approaches are included in this assessment.*

1.3 Topline statements

Applicability of PAVR for current nonsurgical candidates

The best evidence comes from early uncontrolled case series. This kind of evidence for new technologies often suggests a promising outlook, which may or may not be borne out by later, more robust trials. In the case of percutaneous aortic valve replacement (PAVR) for this population of patients, there are grounds for cautious optimism. These patients have no substantively effective alternatives. Also, while the procedure carries significant and life-threatening risks, the condition itself is associated with a very poor prognosis and severe functional limitation. Studies demonstrate that PAVR has substantially improved symptoms, at least in the short term, in some patients. Many patients and professionals might, therefore, regard the procedure as a risk worth taking.

From a population perspective, there are additional considerations. Costs are substantial, with inadequate data to compare with costs of conventional management, or to compare how those costs will be distributed among stakeholder budgets. Longer term clinical benefits have yet to be assessed, and it may turn out that such benefits are marginal or even absent. These facts, and opportunity costs of favouring this procedure over competing calls on resources, should be borne in mind when formulating policy.

Given these considerations, a possible approach to adoption is to prioritise the procedure for nonsurgical candidates using an agreed risk stratification tool which balances the benefits and risks in this population. This should be done under conditions of careful and thorough informed consent and documented in a registry that permits ongoing assessment of case mix, effectiveness, costs and cost distribution. Demand in East Midlands SCG under these circumstances is unlikely to exceed 50 patients over 75 years old per annum, at a modelled total cost of £900,000 per year.

Any policy should be revisited in light of forthcoming research data, technological refinements and procedural experience.

Applicability of PAVR for surgical candidates

The situation in this population, including those with borderline eligibility for open procedures, is different. There is not yet enough evidence to support PAVR with this group. We found no published data (uncontrolled or otherwise) on PAVR specifically in this group for whom, by definition, an established alternative exists (open heart surgery). In our opinion, adoption in this population should only take place in the context of, or pending positive clinical results from, a

robust (preferably multicentre) randomised controlled clinical trial. One such trial is underway and will be completed in 2014. Preliminary results may be available sooner (see section 1.5).

Again, any policy will need to be revisited in light of developments in technology and the evidence base.

1.4 Supporting statements

Current nonsurgical candidates

Effectiveness

- We found low level evidence from case series regarding the use of percutaneous aortic valve replacement (PAVR) for people with severe aortic stenosis who are refused open heart surgery. More robust evidence will be available when the results of an ongoing RCT are available towards the end of 2008.
- These patients have a poor prognosis and high mortality with conventional management, including medical therapy (62% survival at one year[3,4]) or alternatives such as balloon valvuloplasty. In this population, retrograde PAVR improves haemodynamics (valvular dimensions and transaortic pressure gradient) and clinical symptoms from pre-procedural levels. In those who survive, these improvements are maintained in the medium term. Thirty day mortality ranges from 12 to 20%. Longer term results are not available, but given the thirty day statistics, one year survival in these series will not exceed 80 to 88%.
- PAVR is associated with risks, some of which are life threatening. At this stage it is difficult to reliably quantify these risks, but the rates are significant. The risks are likely to decline with increasing surgical skills and refinements in the device and insertion techniques.

Demand

- If limited to current nonsurgical candidates, about 50 patients aged over 75 years will be eligible for PAVR each year in the East Midlands SCG region. Across the whole of England there will be approximately 600 eligible cases each year. This demand will be shared between providers in the North and South. There are caveats associated with these estimates due to the assumptions that underpin them (see section 3).

Cost effectiveness

- We found no cost effectiveness studies of this technology. In any case, effectiveness data are not yet robust enough to lend credibility to any cost-effectiveness models, were they available.

Cost

- Based on our estimates of annual demand, we estimate that the cost of providing PAVR in the East Midlands regions to current nonsurgical candidates over age 75 years will be £900,000 each year. There are caveats associated with this model (see section 3).

Patient prioritisation

- It should be noted that there are different ways to define "nonsurgical candidates." There are also different ways of stratifying risk among those with aortic stenosis, in order to prioritise them for PAVR. One widely used system is the EuroSCORE (logistic or additive). However there are limitations to its use as it has not been validated specifically for this procedure. In addition, it does not take into account practical factors such as femoral atherosclerosis or vessel tortuosity which make some patients unsuitable.

Current surgical candidates

Effectiveness

- To date there are no studies investigating PAVR in patients who are candidates for open heart surgery.

Demand

- If in future PAVR is also indicated for those who are currently offered surgery, then in total approximately 1,800 patients (which includes current nonsurgical candidates) aged over 75 years will be eligible each year across England. 155 of them are from the East Midlands SCG region. It is unlikely that this will be the case in the medium term. There are caveats associated with this model (see section 3).

Cost effectiveness

- We found no cost effectiveness studies of this technology.

Cost

- We have not modelled cost for patients who are currently referred for surgery.

1.5 Future developments - what to watch

The field of PAVR is in a phase of rapid research and development. We are aware of several initiatives that may be triggers to revisit policy:

1. NICE: An interventional procedures overview of transcatheter aortic valve implantation for aortic stenosis has been out for public consultation and is currently being finalised by NICE. It will be published this summer.[5]

2. The PARTNER-US trial (ClinicalTrials.gov identifier: NCT00530894): A randomised controlled trial has begun in the USA (also including a German centre) and is currently recruiting patients with severe symptomatic aortic stenosis who are a) at high risk for open heart surgery and b) not surgical candidates. The study will compare the Edwards Valve with open surgery for the first group and with best supportive care for the second. The original plan for this study was to recruit 600 participants, though this has recently been increased to 1040 with the addition of the Ascendra system (a transapical valve) to the list of interventions. The study will be completed in September 2014 though preliminary results may be available sooner as there are follow ups for participants at 30 days, 6 months and 1 year. It will provide the only evidence to date on:

- The differences between the Edwards valve and surgical valve replacement in people at high risk
- How percutaneous transplant with the Edwards valve compares to medical treatment in non surgical candidates

The details of this study have changed since our original draft of this report so it is advisable to keep up to date with the entry at http://clinicaltrials.gov/ct2/show/NCT00530894

3. Longer term follow up of the initial patient series will provide more information on the durability and long term efficacy of the percutaneous devices.

4. New technologies are in development. Manufactures will learn from the experience of the Edwards and CoreValves and make refinements to their devices and delivery methods that will no

doubt improve clinical outcomes for patients. Examples include Direct Flow device (Santa Rosa), Lotus device (Sadra Medical), and Paniagua Heart Valve (Endoluminal Technology Research).

Section 2 - The Evidence

2.1 Background to the evidence

Clinical context

Calcific aortic stenosis is common in older people and prevalence is increasing with the ageing population. In 2005-2006 there were 10,396 diagnoses of aortic stenosis; 37% of these in patients aged between 60 and 74 years and 50% of these in patients aged over 75 years, in whom the overwhelming majority will be for calcific aortic stenosis.[6]

Figure 1: Diagnoses of aortic stenosis in England[6]

Measures of disease severity (jet velocity, LV function, valve area) and physical symptoms are not well correlated.[1,3] Adults with haemodynamically 'severe' disease can be asymptomatic with a good prognosis.[3] However, the onset of symptoms, which include angina, syncope and breathlessness associated with heart failure, is an important point in the natural history of the disease. Onset of angina and syncope is associated with an average survival of 2 to 3 years, and congestive heart failure with an average survival of 1.5 to 2 years.[3] As a result of the correlation between symptoms and prognosis, therapeutic decisions, particularly related to surgery, are based on the presence or absence of symptoms.

Treatments for aortic stenosis

Guidelines suggest that open aortic valve replacement (AVR) should be considered in virtually all symptomatic patients with severe aortic stenosis.[1] AVR is also indicated for patients with moderate-severe aortic stenosis undergoing coronary artery bypass graft (CABG) or other cardiovascular

surgery or in some cases if replacement is seen as appropriate after exercise testing. Without valve replacement, symptomatic patients with severe aortic stenosis are unlikely to survive beyond three years.[3]

Operative mortality with open heart aortic valve replacement is about 3-6%, and is higher (8 to 15%) in octogenarians.[7-10] A UK heart valve registry study found that 30 day mortality with AVR was 6.6%.[3] Mortality is likely to be greater in patients with more severe disease. Medical therapy is not very effective and balloon valvuloplasty, though offering transient palliative benefits has a high intra-operative mortality and poor survival at one year.[3] Considering the prognosis of symptomatic disease, conventional open heart aortic valve replacement is a reliable treatment.[9] Some patients will not be suitable candidates as it involves major surgery (lasting around two to four hours) and cardiopulmonary bypass which poses an unacceptable risk in those with advanced age and significant comorbidities. The Euro Heart Survey on valvular disease, carried out across 25 European countries on 5,000 people, found that 32% of people requiring surgery for severe valve disease were not referred.[2] This is likely to be because of their high peri-operative risk. The study confirms that the decision not to operate was associated with older age, lower ejection fraction and with neurological comorbidity.[2,11]

The EuroSCORE is a risk stratification tool that is often used to assess patients for valve replacements. It was originally designed to predict operative mortality in people undergoing coronary artery bypass surgery. There are additive and logistic versions that assign weights to seventeen adverse risk factors, such as age, left ventricular dysfunction, creatinine level. It has been validated in several countries and predicts long term outcome following open heart surgery and open heart valve procedures.[12] There is some doubt as to whether it is calibrated accurately enough to predict mortality in the high risk groups considered for PAVR.[12] In a subset of high risk patients offered isolated surgical valve replacement with a predicted hospital mortality of 17.2%, the actual hospital mortality was 7.8%.[12]

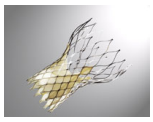
In patients currently denied surgery, less invasive valve replacement procedures such as those using percutaneous delivery may provide a safer alternative. The procedures can be carried out under general anaesthesia or local anaesthesia with or without sedation. Patients do not require open heart surgery, though haemodynamic support (femoro-femoral bypass or ventricular assist device) may be used. Rapid ventricular pacing is required during the procedure to reduce cardiac output while the implant is stabilised. The percutaneous replacement involves imaging-guided insertion of

a catheter through the femoral artery (retrograde/transluminal) or vein (antegrade). The retrograde approach is considered less complex as it does not require puncture of the interatrial septum. The retrograde approach is the more popular delivery method, and is the sole focus of this report. Prior to valve placement, it is common to advance a balloon catheter into the left ventricle over a guidewire to pre-dilate the opening of the aortic valve to make room for the prosthesis. The delivery catheter carries a bioprosthetic aortic valve to the site which, when deployed, replaces the diseased native valve. The deployment method depends on which prosthesis is used; CoreValve is self-expanding while the Edwards valve is inflated using a large balloon.

Current percutaneous devices

The two most widely used devices are the CoreValve Revalving System and the Edwards (Cribier-Edwards) valve. In these early days of the technology and in the absence of data comparing the two, selection between them is likely to depend on a centre's preference and experience of the interventional cardiologist. The table below describes their key features.

Table 1: Devices for percutaneous aortic valve replacement

Device name	Manufacturer		Insertion
Edwards valve (first generation: Cribier-Edwards equine valve, second generation: Edwards-Sapien bovine valve)	Edwards Lifesciences, Irvine, California	 First generation equine valve on stainless steel frame  Second generation bovine valve on stainless steel frame	Either retrograde or antegrade delivery possible; device is balloon-expandable; antegrade surgery is more risky as it involves puncture of the interatrial septum. First generation used equine valve tissue, second generation uses bovine tissue. Temporary rapid ventricular pacing (>200bpm) may be used to provide haemodynamic stability during placement.
CoreValve's Revalving System (first generation: bovine valve, second generation: porcine valve)	CoreValve, Inc., Irvine, California	 Self-expanding valve (tissue on nitinol frame)	Retrograde delivery; self-expanding from nitinol frame; first generation bovine trileaflet valve delivered through 25French (F) catheter; second generation porcine trileaflet valve delivered through 21F catheter; third generation porcine trileaflet delivered through 18F catheter. Clinical protocol requires some form of cardiac assistance, usually femoro-femoral cardiopulmonary bypass or a percutaneous left ventricular assist device (e.g. Tandem Heart).

Several other devices are in development and manufacturers will learn from the experience so far with the Edwards and CoreValves. Examples include Direct Flow device (Santa Rosa), Lotus device (Sadra Medical), and Paniagua Heart Valve (Endoluminal Technology Research). These devices are at a much earlier stage of research and development, with negligible human data. This review is therefore limited to the Edwards and CoreValves devices. Refinements to existing devices and improvements in design and delivery methods will aim to improve clinical outcomes for patients. It will be important for commissioners to keep up to date with these developments.

2.2 Evidence details

We searched for all studies of percutaneous valve replacements in people with aortic stenosis. As the technology is still in development we did not exclude any studies on the basis of study design. We limited our analysis to the retrograde delivery method. We found:

- Five case studies[13-17]
- Seven case series (9 publications)[18-26]

The results are discussed separately for the Edwards valve and the CoreValve. See data extraction tables (section 2.4) for further details.

2.2.1 The Edwards valve

Our review identified two case studies[13,15] and two case series[21,25] of the Edwards valve, a total of 88 patients.

Evidence about short term effectiveness:

Insertion success (case series only): Two of two case series reported this outcome.[21,25]
The device was inserted successfully in 4/7 [57%], and 43/50 [86%] in two case series.[21,25] In the three failures in the first series, the stent-mounted catheter was too short to reach the valve in one, and extensive calcification prevented retrograde implantation in the other two failures.[21] In the second series, reasons for the seven failures were: inability to pass the iliac artery in one, inability to cross the native valve in three, a defective catheter in one and malpositioning in 2 patients.[25]

Haemodynamic improvement: Two of two case series and both case studies reported this outcome.[13,15,21,25]
The first series did not provide echocardiography results separately for those patients who underwent a retrograde delivery, though notes that in those who had successful implants and survived to 2 years, haemodynamic improvements were sustained.[21] In the second series, there was an immediate overall reduction in mean transaortic gradient (46 v 11mmHg; $p<0.001$) and an increase in mean valve area (0.6cm^2 v 1.7cm^2; $p<0.0001$).[25] LVEF improved significantly within days (53% to 57%) and all haemodynamic improvements were maintained up to one year in survivors. Immediate postoperative haemodynamic improvements were also noted in the two additional case reports.[13,15]

Improvement in symptoms: Two of two case series reported this outcome.[21,25] There was limited information from the case studies.[13,15] The first series did not report results separately for the

retrograde delivery; however, it says that in those with successful implantation there was 'remarkable amelioration of symptoms'.[21] This persisted in those (11/27) who survived to nine or more months.[21] In the second series, 50% of successful placements had improved by ≥1 NYHA class after 30 days.[25] This improvement was maintained at 6 and 12 months follow-up, however the time trend was not significant.[25] In the first case study a peri-procedural complication resulted in respiratory failure and cardiac arrest and ultimately death on day five.[15] The second case report, though providing limited results of follow-up, states that the patient remained symptom free at 12 months.[13]

Mortality at 30 days: All studies reported on this outcome.[13,15,21,25] The first series did not report on results separately for those receiving retrograde delivery, though reports 26% MACCE (including death) at 30 days.[21] In the second case series of the Edwards valve, 6/50 [12%] of patients had died by 30 days.[25] In one case study, the patient died at five days due to complications related to previous attempt at antegrade delivery.[15] In the second case report, the patient was 'symptom free' at 12 months.[13]

Long term clinical outcomes:

We found no studies that reported clinical outcomes beyond two years.

Procedural learning curve:

The largest case series (50 patients) compared the outcomes of the first 25 patients with the second 25 patients. It found that the rates of procedural success increased (76% v 96%; p=0.10), malpositioning fell (8% v 0%) and fewer people died during the procedure in the later half of the series (4% v 0%). 30-day mortality was also reduced (16% v 8%; p=0.39).[25] This pattern of results suggests an improvement in outcomes over with procedural experience.

Evidence about safety:

Procedure-related complications: Two of two case series[21,25] and one case study reported this outcome.[15] The first series did not provide results on complications for retrograde delivery separately from antegrade, however reports that 6 of 27 patients experienced a complication during the procedure (two died as a result of cardiac tamponade, one with a trans-septal puncture, one with a perforated ventricle).[21] In the second series (50 patients), there was one intra-procedural death due to aortic injury.[25] There were five post-procedural deaths within 30 days of the operation, due to: ventricular arrhythmia, left main occlusion, iliac injury, stroke, and multiorgan failure.[25]

Some of these complications were related to the procedure.[25] Iliac injury requiring major vascular repair occurred in three patients, one resulting in death.[25] In a third patient, the abdominal aorta was perforated resulting in mortality.[25] Access site infections occurred in two patients after complex vascular closure and they were treated with antibiotics. Peri-procedural stroke occurred in two patients; one died at 29 days, the other completely recovered.[25]

In the first case report, the antegrade approach was attempted first. During the procedure, the guidewire became snared in the left iliac artery and tethered the anterior mitral valve leaflet during attempts to externalise the guidewire through the common femoral artery.[15] Despite a successful subsequent retrograde insertion, the patient rapidly declined, experiencing respiratory failure, cardiac arrest, hypotension, aortic regurgitation, sever mitral regurgitation and occluded coronary arteries. He died on day five.[15] Autopsy revealed a guidewire-induced laceration on the anterior mitral valve leaflet.[15]

2.2.2 The CoreValve

Our review identified three case studies[14,16,17], five case series (six publications).[18-20,22-24,26] In total 139 patients were included.

Evidence about short term effectiveness:

Insertion success (case series only): Three of five case series reported this outcome clearly.[20,22,24,26] In one series, the device was inserted successfully in 22/25 [88%] [22] of patients and in two series insertion was 100% successful.[20,24] In another the device was implanted successfully in 76/86 [88%][26] of patients. One case series (four patients) did not provide insertion success results.[23]

Haemodynamic improvement: All case series and case studies reported this outcome.[14,16,17,20,22-24,26] Improvement in valve area and transaortic pressure gradient was immediate and significant in all cases (results were unclear for 3 of 4 patients in one series[23]). Two case series (25 patients and 11 patients) found that these improvements were sustained 30 days after discharge in those who were available for follow up (60% in first study, unclear in second).[20,22] The other series did not report on haemodynamic variables other than those encountered intra-operatively.[23,24,26]

Improvement in symptoms: Four of five case series[20,22,24,26] and two of three case studies reported this outcome.[14,17] The third case study stated that the patient 'felt well'.[16] Four of five case series reported improved symptoms at 30 days in survivors.[20,22,24,26] The improvement in symptoms

amounted to at least one grade on the New York Heart Association scale in most of the surviving patients. The three case studies indicate that symptom improvement remained at 14 days,[14] 3 months,[17] and one with unclear follow up.[16]

Mortality at 30 days: Three of five case series reported this outcome.[20,24,26] 30 day mortality in one series was 18% overall.[20] The largest case series of this valve (86 patients) found that 30 day mortality was 12% (combined rate of death, stroke and MI 22%).[26] In a third series, 30 day mortality was 20% and 3 month mortality was 30%.[24] The case studies had limited or unclear follow up, though one reports on a live patient at 30 days.[17]

Long term outcomes:

We found no studies that reported clinical outcomes beyond two years.

Technological improvements:

The largest case series of the CoreValve (86 patients) compared use of 21F v 18F delivery catheter and found significantly improved outcomes with the latter. This analysis, though it may have been confounded by learning curve effects, raises the point that device refinement will likely improve outcomes for patients.

Evidence about safety:

Procedure-related complications: Four of five case series reported on complications.[20,22,24,26] There were placement problems in 2/25 [8%] of patients in one case series (device not deployed deeply enough), both requiring open heart surgery to retrieve the device and replace the valve conventionally. Both patients were then event free at 30 days.[22] In one patient the device could not be inserted despite successful predilation with a 23mm balloon and sudden death followed 12 hours later.[22] Perforation of the left ventricle resulted in death in another patient in this series.[22] All patients in this series developed thrombocytopenia.[22] Postprocedural complications in one series (of 11 patients) were limited to left bundle branch block and thrombocytopenia in one patient and access site infection in another.[20] In this series one patient suffered a fatal procedure-related stroke due to displacement of vascular tissue that led to occlusion of the left subclavian artery.[20] Reasons for failure in another series included failure to cross heavily calcified valves, and suboptimal placement.[26] Some studies report aortic regurgitation following placement, though overall rates are difficult to determine.

One series provided very limited results about patients and no results about complications.[23] In one series (10 patients), two patients required percutaneous angioplasty of the common iliac artery to allow sheath progression. In a third, vascular tissue was displaced by catheter advancement resulting in subsequent haemorrhagic shock.[24]

2.3 Evidence summary

2.3.1 Effectiveness

Current nonsurgical candidates

- We found seven case series that consistently showed immediate haemodynamic improvement (increased effective valve area, reduced transaortic pressure gradient) in people in whom the device was inserted successfully and who did not die during surgery. The improvements in most were maintained up to 30 days after valve replacement.

- Symptomatic relief was associated with haemodynamic improvement in most studies (by an average of one class on the NYHA scale). Improvements were maintained at 30 days and in some cases up to 12 months after intervention.

- Almost all clinical data (morbidity, mortality) was limited to 30 days. There are no outcomes reported beyond 2 years.

- The procedure is associated with placement problems that may require rescue open heart surgery and harms including vascular injury, access site infections, thrombocytopenia, paravalvular insufficiency and stroke. At this stage it is difficult to reliably quantify these risks, but the rates are significant.

- In the five case series that assessed this outcome, 30-day mortality rates ranged from 12 to 20%. In these series, patients had a pre procedure EuroSCORE suggesting that their hospital mortality from open heart AVR could be up to 36% (ranged from 22% to 36%, with one reporting mean additive score of 12).

- We found no studies comparing percutaneous aortic valve replacement with alternatives (e.g. medical therapy, balloon valvuloplasty) in patients with severe symptomatic aortic stenosis who are unsuitable for surgery.

- There is evidence from one series that patient outcomes improve in a centre with procedural experience and from another that device refinements (reduced catheter diameter) improve clinical outcomes.

Those currently offered surgery:

- We found no evidence from published literature on the use of percutaneous valve replacements in people who are currently considered suitable for open heart surgery.

2.3.2 Cost effectiveness

- We found no cost effectiveness studies.

2.3.3 Patient prioritisation

- All study participants were described as being 'unfit for surgery' though the definition of this varied. Overall, all patients were extremely high risk with severe heart failure symptoms (NYHA III or IV), significant comorbidities (commonly coronary artery disease), with logistic EuroSCOREs ranging from 11% to 36%.

- The logistic EuroSCORE which includes age as an input might be used as a basis for prioritising patients for this procedure. However there are limitations to its use as it has not been validated specifically for PAVR. In addition, it does not take into account practical factors such as femoral atherosclerosis or vessel tortuosity, which make some patients unsuitable.

2.4 Data extraction tables

Reference and study design	Population	Procedure	Outcomes and follow up (% followed up)	Findings	Notes
Edwards valve					
Hanzel et al, 2005[15] Case study (Edwards valve: first retrograde implantation)	Case study: 84 year old man with critical aortic stenosis, severe symptoms (NYHA class IV heart failure), mean transvalvular pressure gradient 29mmHg, aortic valve area 0.64cm^2, left ventricular ejection fraction (LVEF) 20%, ventricular tachycardia (implantable cardiac defibrillator *in situ*). Unfit for surgery. Significant comorbidities including coronary artery disease (CAD), CABG surgery, multiple PCIs, paroxysmal atrial fibrillation, left nephrectomy (renal cell carcinoma), end-stage renal disease, renal tubular acidosis, hypertension, hyperlipidemia, chronic anaemia, hypothyroidism, gout.	Antegrade approach attempted first (abandoned after mitral valve became tethered in guidewire resulting in pulseless electrical activity and requiring resuscitation). Retrograde approach via iliac artery using 22mm balloon. Rapid right ventricular pacing was used to decrease cardiac output.	i. aortic valve area ii. transvalvular pressure gradient iii. regurgitation Follow-up: Immediately post-procedure, 1 day, 2day, 3 day, 4 day	i. **aortic valve area**: increased immediately post-deployment (0.55cm^2 before v 1.7cm^2 after), maintained at day 1 (1.7cm^2) ii. **pressure gradient**: reduced (45mmHg before v 4mmHg after), maintained at day 1 (no pressure gradient) iii. **regurgitation**: mild paravalvular aortic regurgitation, moderate mitral regurgitation (worsening from baseline) *Day 2*: respiratory failure and cardiac arrest following extubation. Intra-aortic balloon pump was inserted *Day 3*: ventricular tachycardia, electrically cardioverted *Day 4*: worsening hypotension, moderate paravalvular aortic regurgitation, severe mitral regurgitation, LVEF 10%, occluded coronary arteries (left anterior descending and right) *Day 5*: pulseless electrical activity and death	Interpretation by authors: technically successful retrograde implantation. Death was likely due to complications associated with initial antegrade approach.
Cribier et al, 2006[21] Case series (Edwards valve: mid-term follow-up from initial feasibility studies in Rouen, France;	Case series: 36 elderly patients with severe, symptomatic (NYHA class IV) aortic stenosis, aortic valve area ≤0.7cm^2, average age 80 years, 57% male, majority with LVEF 31-50%, significant comorbidities (76% had CAD). Unfit for surgery. The specific characteristics of those who subsequently underwent the retrograde procedure are not separated from a description	Retrograde approach (attempted in 7/33 patients) via femoral artery (predilated) using 22mm balloon. Rapid ventricular pacing used during procedure.	i. insertion success ii. complications iii. MACCE▾ at 30 days and 6 months (overall) iv. symptoms v. survival vi. echocardiographic	i. **insertion success rate**: 4/7 [57%] successful implantations in retrograde procedure (in the three failures: stent-mounted catheter was too short to reach valve in one, and in remaining two, extensive calcification prevented retrograde implantation) ii. **complications (no separate results for retrograde)**: during the procedure, 6 of 27 patients with successful antegrade or retrograde implantation had a complication (two died from cardiac tamponade, one - taking long term steroids - developed	Description of study population and most of the results were not separated by the type of procedure (i.e. antegrade or retrograde). Researchers conclude that it was 'easier to cross the native valve with the [prosthesis] in

▾ MACCE: major adverse coronary and cardiovascular events

Reference and study design	Population	Procedure	Outcomes and follow up (% followed up)	Findings	Notes
the I-REVIVE/RECAST trials) Most results do not separate out retrograde and antegrade	of the entire series. Mean EuroSCORE 12(+/-2); mean Parsonet's score 49 +/- 7.		results Follow-up: 1, 3, 6 and 12 months (then 6 monthly thereafter)	urosepsis, one with complete heart block and prolonged resuscitation leading to brain damage, one developed a stroke and later died at 33 days due to multi-organ failure, one had intractable hypotension following removal of the 24F sheath) iii. **MACCE at 30 days and 6 months (no separate results for retrograde)**: 7/27 [26%] at 30 days (some deaths were related to complications from the procedure, but not to device failure); 10/27 [37%] MACCE at 6 months (excluding MACCE at 30 days). None of the deaths between 30days and 6 months were due to device related complications. iv. **symptoms (no separate results for retrograde)**: in 21 patients with successful implantation, there was 'remarkable amelioration of symptoms' which persisted in those who survived to 9 or more months (longest follow up is 26 months) v. **survival (no separate results for retrograde)**: 11/21 [52%] at end of study (follow up ranged from 9-26 months) vi. **echocardiographic results (no separate results for retrograde)**: no significant change in valve area and mean transvalvular gradient at 3 to 24 months in the 11 who had successful implants (valve area: 1.72cm² before v 1.69cm² after; transvalvular gradient: 9mmHg before v 11mmHg after)	the antegrade rather than the retrograde direction, particularly in patients with excessive calcification.' The retrograde approach was reportedly quicker and less technically demanding. However, many patients were not suitable candidates for this approach because of diseased femoral arteries.
Chandavimol et al, 2006[13] Case study (Edwards valve: first successful North American	Case study: 85 year old man with severe symptomatic (NYHA class III) aortic stenosis, mean transvalvular pressure gradient 58mmHg, valve diameter 25mm, mild mitral regurgitation, left ventricular hypertrophy, normal left ventricular systolic function, at unacceptable risk	Retrograde approach through femoral artery. Rapid pacing (200bpm) used to decrease cardiac output while prosthesis was being stabilized.	i. valve area ii. transvalvular pressure gradient iii. symptoms Follow-up:	i. **aortic valve area**: improved at 1 month (1.8cm²) ii. **pressure gradient**: reduced at 1 month (58mmHg before v 16mmHg after) iii. **symptoms**: patient remained symptom free after 12 months of clinical follow-up	Very limited results in this study

Reference and study design	Population	Procedure	Outcomes and follow up (% followed up)	Findings	Notes
procedure) Very limited results in this study	with traditional surgical valve replacement. Significant comorbidities including CABG (repeat five years previously), coronary stenting, hypertension, smoking, hypercholesterolemia, chronic myelomonocytic leukemia, hypothyroidism.		1 month, 12 months		
Webb et al, 2007[25] Case series Edwards valve (Early results of first 18 patients in series were published separately, Webb et al, 2006[27] and are not reported here)	Case series: 50 symptomatic patients at 'excessively high risk' for conventional surgery; mean age 82.7years, comorbidities included CAD, moderate/severe mitral regurgitation, lung disease, severe debility. Mean logistic EuroSCORE 28%. Exclusions: diameter of aortic annulus <18 or >26mm, iliofemoral arterial disease, comorbidities likely to reduce quality of duration of life despite AVR.	Cribier-Edwards valve (23mm or 26mm); transcatheter implantation through femoral artery (retrograde) 'usually under general anaesthetic with endotracheal intubation'. Cardiopulmonary bypass not used. Fluoroscopy, aortography, and transoesophageal echocardiographic imaging (TOE) used to confirm position.	i. insertion success ii. mortality rate iii. survival rate iv. functional improvement (NYHA class) v. echocardiographic results vi. complications Follow-up: 1month, 6 months (100%), 12 months (>50%)	i. **insertion success**: 43/50 [86%], failure due to inability to pass the iliac artery in one, inability to cross the native valve in 3, a defective catheter in one and malpositioning in remaining 2 patients ii. **mortality rate** (30 days): 12% iii. **survival rate** (as a proportion of successful procedures): 38/43 [88%] at 1 month, 35/43 [81%] at 6 months, 17/43 [40%] at 12 months iv. **functional improvement**: 50% of successful replacements had improved by ≥1 NYHA class after 30 days improvement maintained at 6 and 12 months (non-significant time trend; p=0.59) v. **echocardiographic results**: - immediate reduction in mean transvalvular pressure gradient (46 mmHg before v 11mmHg after; p<0.001) - immediate increase in mean valve area (0.6 before v 1.7 cm^2 after; p<0.0001) - improvements maintained up to 1 year - increase in LVEF 'within days' (53% to 57%; p<0.0001) - improvement in LVEF sustained up to 1 year (non-significant	First 25 patients in the series had worse outcomes than next 25 (success rates: 76% v 96%, p=0.10; malposition 8% v 0%, intraprocedural mortality at 30 days: 4% v 0%). Improvement in LVEF was mainly due to that seen in patients with moderate/severe LV dysfunction. Two authors (Webb and Munt) are consultants to Edwards Lifesciences Inc.

Reference and study design	Population	Procedure	Outcomes and follow up (% followed up)	Findings	Notes
				time trend; p=0.80) – sustained improvement in mitral regurgitation (non-significant time trend; p=0.52 up to 12 months) vi. **complications**: – one intraprocedural death (aortic injury) – five postprocedural deaths within 30 days (ventricular arrhythmia, left main coronary artery occlusion, iliac injury, stroke, multiorgan failure) – three post-procedural deaths after 30 days (day 56: respiratory failure, day 71: MI, day 98: renal failure) – aortic insufficiency: non-significant increase in mean grade (0/none, trivial to 1/mild; p=0.57) – no patient with prosthesis had more than mild aortic insufficiency – 'most patients did have some degree of paravalvular insufficiency' (mainly mild, three with moderate) – subsequent reattempt at valve procedure: 3/50 (following unsuccessful transcatheter approaches and continued symptomatic stenosis), one by conventional surgery, one transapical approach and one repeat transfemoral	

CoreValve					
Grube et al, 2005[14] Case study (CoreValve 25F)	Case study: 73 year old woman with severe symptomatic (NYHA class IV) aortic valve stenosis, mean transvalvular gradient 45mmHg, valve area 0.7cm^2, LVEF 45%. Unfit for surgery.	Retrograde via common iliac artery, following surgical cut-down, using first-generation CoreValve (bovine leaflet, 25F catheter). Extracorporal circulation (femoro-femoral bypass).	i. transvalvular pressure gradient (mean and max) ii. symptoms iii. left ventricular	i. **pressure gradient**: immediate reduction (mean: 45mmHg before v 8mmHg after), which persisted at 48 hours (mean: 9.5mmHg, max: 14.5mmHg) and 14 days (mean: 10mmHg, max: 21mmHg) ii. **symptoms**: by day 8, patient was discharged and NYHA improved (grade IV before surgery to grade II after surgery)	

	Significant comorbidities, including previous CABG, prior MI, renal insufficiency, breast cancer.		function Follow-up: Immediately post-procedure, 1, 2, and 14 days	By day 14, patient reported significantly improved quality of life. iii. **left ventricular function**: increase in LVEF at 48 hours (45% to 76%); normalized at day 14. No evidence of valvular or paravalvular regurgitation.	
Grube et al, 2006[22] Case series (CoreValve: the Sieberg First-in-Man study)	Case series: 25 symptomatic patients, mean age 80.3 years, mean (SD) transvalvular pressure gradient 44.2+/-10.8mmHg, mean aortic valve area 0.72+/-0.13cm^2, aortic regurgitation present in 68%, 96% with severe symptoms (NYHA class III or IV), median logistic EuroSCORE was 11% (interquartile range 9.2% to 19.9%), mean additive EuroSCORE 9.0 (+/- 2.3).	Retrograde approach via common femoral artery in 13 patients using second-generation CoreValve (porcine, 21F catheter); via common iliac artery, following surgical cut-down, in nine patients; via subclavian artery in three patients. Iliac and subclavian approaches used first generation valves (bovine, 24F catheter) in ten patients and second generation valves in two. Performed under TOE guidance and with extracorporal circulation (femoro-femoral bypass).	i. insertion success ii. haemodynamic valve performance iii. complications iv. MACCE▾ v. clinical symptoms Follow-up: 30 days post-discharge (60%) 180 days (7/30) 365 (2/30)	i. **insertion success**: 22/25 [88%] ii. **haemodynamic valve performance**: - aortic regurgitation: (grade 0.86+/-0.73 before v 0.71+/-0.78 after procedure; p>0.05) - mean pressure gradient: (44.24+/-10.79mmHg before surgery v 12.38+/-3.03mmHg after v 11.82+/-3.42mmHg at 30 day follow up; p<0.0001 for pre v post surgery; p =0.83 for post-surgery v 30 days) - peak pressure gradient: (69.90+/-22.96mmHg before surgery v 21.31+/-5.05mmHg after v 22.10+/-3.61mmHg at 30 days; p=0.30 for post-surgery v 30 days) iii. **complications**: - placement problems: in 2/25 [8%], there was significant paravalvular leakage (due to incorrect deployment in relation to the native valve) and urgent open heart surgery ensued with successful device retrieval and implantation with conventional mechanical valve. Both patients were event-free at 30 days - device could not be inserted in 1/25 patients despite successful prior balloon valvuloplasty; sudden death followed 12 hours after the procedure	High insertion success rate. Non-significant improvement in aortic regurgitation grade

▾ MACCE: major adverse coronary and cardiovascular events

				– 1/25 additional patient died 12 hours after the procedure from wire perforation of the left ventricle – thrombocytopenia: all patients developed thrombocytopenia, fatal disseminated coagulation in 1 of 3 patients with severe thrombocytopenia (in whom loading dose of clopidogrel had been omitted) iv. **MACCE***: in-hospital mortality 5/25 [20%] overall, two outlined above and three additional deaths on days 9, 13, and 15. One experienced minor stroke, major bleeding occurred in 5/10 [50%] treated with first generation device, and 1/15 [6.7%] treated with second generation device v. **clinical symptoms**: of 18 who survived to discharge, all had improved clinical symptoms at 30 days (17 with NYHA class III and one with NYHA class II before v 12 with NYHA class II and six with NYHA class I after) Ongoing follow up is continuing to 4 years. Of eight patients available for180 or 365 day follow-ups, one patient developed left ventricular failure, eight are clinically unchanged and one is unreported	
de Jaegere et al, 2006[16] Case study (CoreValve 25F: first Netherlands patient)	Case study: 77 year old woman with severe symptomatic aortic stenosis and severe calcification of the ascending aorta and aortic arch, who was declined surgical valve replacement for this reason. Diameter of aortic annulus 23mm. Mild to moderate aortic and mitral regurgitation. Atrial fibrillation on current ECG and thrombus in left atrium on echo. No previous medical history or comorbidity (no	Retrograde delivery via femoral artery under general anaesthesia. Extracorporal circulation using femoro-femoral bypass.	i. regurgitation ii. other events Follow-up: unclear	Balloon valvuloplasty reduced peak-to-peak transvalvular pressure gradient from 43mmHg before to 7mmHg after. i. **regurgitation**: absence of aortic regurgitation following deployment ii. **other events**: delayed wound healing prolonged hospital stay but 'further course was uneventful'. Patient 'felt well' and there were no symptoms or signs that suggested heart failure. Minimal aortic regurgitation on echo, probably due to small paravalvular leak	

	significant CAD).				
de Jaegere et al, 2007[23] Case series (CoreValve 18F: first 'true percutaneous implantation' of CoreValve) Very limited results given	Case series : 4 patients underwent the procedure. The first an 89 year old woman with severe symptomatic aortic stenosis (peak velocity 4.8m/sec, peak transvalvular pressure gradient 92mmHg), moderately impaired systolic LVF. Considered high risk because of age, renal function, so rejected for surgery. Logistic EuroScore of one participant: 19.3%. No significant aortic or mitral regurgitation. No CAD. No previous medical history aside from a hip replacement. Referred for AVR because of rapid progressing symptoms. No details about the remaining 3 patients.	Retrograde delivery via femoral artery under sedation and local anaesthesia. Left-atrial-femoral artery circulatory support using TandemHeart.	i. peak velocity over valve ii. peak transvalvular gradient Follow-up: to discharge (day five)	i. **peak velocity**: reduction in peak velocity over valve in first patient by day five (4.8m/sec before v 2.0m/sec after) ii. **peak gradient**: reduced by day 5 in first patient (92mmHg before v 16mmHg after)	This study describes the first truly percutaneous approach to implantation of the CoreValve. Though there were four patients in the series, results are only given for one patient and even these are limited.
Berry et al, 2007[20] Case series (CoreValve 21F) Berry, Cartier & Bonan, 2007[19] (detailed report of one fatality in this series) Berry et al, 2006[18]	Case series: 11 patients with severe symptomatic aortic stenosis (NYHA class III and IV), average age 82 years, 'believed to be nonsurgical candidates or who had been declined surgical aortic valve replacement'. Mean (SD) AV area 0.56cm² (+/-0.19cm²), mean LVEF 49% (+/-17%). One patient underwent AVR combined with simultaneous PCI. Median logistic EuroSCORE 36% (5-48%); 77% with a logistic EuroSCORE >20%	Retrograde delivery. Authors define some 'novel adjunctive procedural techniques': peripheral transluminal angioplasty (to predilate nonpermissive ilio-femoral arteries), ad hoc PCI in one patient, novel anaesthetic management (intubation with patient 'asleep' except in one using topical local anaesthesia to permit intubation while awake), TandemHeart was used to maintain extracorporeal circulation.	i. insertion success ii. mortality at 30 days iii. symptoms iv. aortic valve area v. pressure gradient vi. in-hospital mortality vii. complications Follow-up: 30 days, until study	i. **insertion success**: 11/11 (100%) ii. **30-day mortality**: 2/11 (18%) iii: **symptoms**: improved at 30 days compared to baseline (by NYHA functional classes in one patient and by one functional class in all others; p=0.006) iv. **aortic valve area**: significant improvement in valve area at one month (0.56+/-0.19cm² before v 1.3+/- 0.4cm² at one month; p<0.0001) v. **pressure gradient**: significant improvement in transvalvular gradient at one month (51+/-19mmHg before v 9+/-4mmHg at one month; p<0.00001)	In a separate publication, Berry et al describe outcomes for an 85 year old man who underwent PAVR. Severe resistance was encountered while advancing delivery catheter through left iliac artery (despite predilation). PAVR was achieved promptly after that. However, following subsequent

(detailed report of one combined PAVR and coronary artery revascularisation in this series)			end (Feb 20, 2007) or death (unclear how many cases were available at each stage)	vi. **in-hospital mortality**: 1/11 [9%] vi. **complications**: after the procedure, one patient had high peak creatinine kinase MB mass concentration (86ug/L) associated with new, persistent left bundle branch block and drop in platelets. Another patient experienced femoral access site infection requiring antibiotics	percutaneous manipulation to remove a left ventricular mass, an embolism of iliac vascular tissue occluded the left subclavian artery and resulted in a fatal right cerebral stroke. In a further publication, Berry et al. describe the case of combined PAVR and coronary artery revascularization in an 85 year old woman with significant comorbidities. Prior to anaesthesia, stenosis in mid-distal segment of left anterior descending artery was observed during coronary angiography. Decision was made to intervene and lesion was predilated and then treated with drug-eluting stent.
Grube et al, 2007[26] Case series (CoreValve 21F and 18F; several of the	Case series: 86 patients (50 with 21F, 36 with 18F), severe symptomatic aortic stenosis (83% with NYHA class III or IV), mean age 82 years. Mean AV area 0.60cm^2 (+/-0.16cm^2), transvalvular pressure gradient 43.7mmHg (+/-15.4mmHg), peak transvalvular pressure	Retrograde, transvascular approach. Initially the 21F device was used in 50 patients (between Aug 2005 and Sept 2006). The 18F device was used from Sept 2006 onwards. Arterial access through standard cutdown of common	i. insertion success ii. procedural success rate (no MACCE within 48h after implantation) iii. 30-day mortality iv. symptoms	i. **insertion success**: 76/86 [88%]. Six patients converted to operative valve replacement, in two the device could not cross the heavily calcified valve, in another two placement was suboptimal and a second device was inserted (prosthesis-in-prosthesis) ii. **procedural success**: 74% (five deaths occurred during the procedure)	Several of the procedures that used the 18F catheter were 'truly' percutaneous, i.e. did not require surgical cutdown.

procedures with an 18F catheter were truly percutaneous.)	gradient 70.9 mmHg (+/-22.8), mean LVEF 54.1% (+/-16.3%), mean logistic EuroSCORE 21.7% (+/- 12.6%).	iliac, common femoral or subclavian artery. Either under general anaesthetic or local with sedative treatment. Use of TOE and type of haemodynamic support left to the operator's discretion.	v. echocardiographic results vi. comparison between 21F and 18F catheters vii. regurgitation Follow-up: post-procedure, discharge, 30 days	iii. **30-day mortality**: 12% (combined rate of death, stroke and MI, 22%) in intention to treat population iv. **symptoms**: decline in mean NYHA functional class at 30 days (2.85+/-0.73 before v 1.85+/- 0.60 after; p<0.001) v. **echocardiographic results**: immediate improvement in transvalvular pressure gradient (mean: 43.7mmHg before v 9.0mmHg after; p<0.001). Aortic regurgitation grade unchanged. No report of valve pressure gradient at 30 days vi. **21F v 18F**: more procedures performed under local anesthesia with 18F (p<0.001); implantations without surgical cutdown more common with 18F (p=0.001); less requirement for haemodynamic support with 18F (p<0.001); significantly reduced procedural time with 18F (because of not needing cardiac assist; p=0.002); no difference in overall success between devices vii. **aortic regurgitation**: in 66% of patients aortic regurgitation remained the same. 20% of patients experienced worsening of regurgitation (to grade 2+) and 14% from 0 to grade 1+. All of these were due to paravalvular leakages.	
Marcheix et al, 2007[24] Case series Corevalve (21F)	Case series: 10 patients with severe symptomatic aortic stenosis (three with NYHA IV, others in class III) referred for percutaneous procedures because of a 'high or prohibitive risk with conventional surgery'. Mean age 81.3 years, 50% male, significant comorbidities (COPD, hypertension, renal insufficiency, CAD, prior CABG, prior mitral valve replacement), median logistic EuroSCORE 32%; 80% with logistic EuroSCORE >20%..	PAVR with CoreValve, using extracorporeal cardiopulmonary bypass support with femoro-femoral bypass. Intraprosthetic balloon dilatation was performed during surgery if there was significant leaking around the valve after insertion.	i. valve insertion ii. mortality (in-hospital 30-day, 30-month) iii. post-procedure echocardiographic and angiography iv. symptoms v. complications vi. valve leak	i. **insertion success**: 100% ii. **mortality**: in-hospital mortality: 30%; 30-day: 20%; 3-month mortality: 30% iii. **echocardiographic results**: immediate improvement in aortic valve area (0.57+/- 0.19cm2 before v 1.2 +/- 0.35cm2; p=0.00001); decrease in transvalvular pressure gradient (mean: 51+/- 19mmHg before to 11+/- 3 mmHg; p<0.001) iv. **symptoms**: NYHA improved by at least one functional class in all surviving patients at 30 days v. **complications**: - two patients required percutaneous angioplasty of the	Authors conclude that mortality was as predicted by Euro and other scores.

			Follow-up: 24 hours, 10 days, one month	common iliac artery to allow progression of the sheath – one patient had intraoperative complications and displacement of iliac artery tissue by catheter advancement; this patient died on day seven after a massive ischeemic stroke – every patient had mild or moderate aortic regurgitation – one patient had postoperative ophthalmoplegia (due to embolic event) – three had transient confusion – two required pacemaker implantation (persistent atrioventricular block) – two had paroxysmal atrial fibrillation – five patients had vascular access complications (haematoma, lymphoceles, required femoral arterial reconstructions) – reoperation was required in two patients (intra-abdominal bleeding related to pericardial and hepatic puncture and another for an infected inguinal lymphocele) vi. **valve leak**: aortic valve regurgitation remained mild immediately AVR and during follow up.	
Lamarche et al, 2007[17] Case study (CoreValve 21F)	Case study: 64 year old woman with critical symptomatic aortic stenosis (NYHA class IV), aortic valve area 0.61cm^2, depressed LVEF (20%), pulmonary hypertension. Predicted operative mortality 10-25%: unfit for surgery.	Retrograde delivery via right femoral artery under local anaesthesia. Use of femoro-femoral cardiopulmonary bypass necessitated exposure of both left and right femoral arteries and left femoral vein.	i echocardiographic results ii. discharge from hospital iii. symptoms Follow-up: immediately post-procedure, three months	i. **echocardiographic results**: improved aortic valve area (0.62cm^2 before v 1.4cm^2 after), improved LVEF (20% before v 35% after) ii. **discharge**: patient discharged on day nine iii. **symptoms**: by three months, 'clinical status was improved but dependent of her pulmonary condition'	

2.5 Table of excluded studies

Study	Reasons for exclusion	Notes
Bauer et al, 2004[28] Case study	Doesn't give any results separately for the retrograde v antegrade approach	Case series: 8 patients with severe aortic stenosis. Significant reduction in mean transvalvular pressure gradient at 24 hours (46mmHg before v 8mmHg after; $p<0.0001$). Significant increase in valve area (0.59cm^2 before v 1.69cm^2 after; $p<0.0001$)
Brinster et al, 2006[29]	Irrelevant procedure ; discusses 'hybrid approach' which is same day PCI and minimally invasive aortic valve replacement (not percutaneous)	
Byrne et al, 2005[30]	Irrelevant procedure ; discusses 'hybrid approach' which is same day PCI and minimally invasive aortic valve replacement (not percutaneous)	
Cerillo et al, 2007[31] Retrospective record review	Discusses outcomes of AVR in the elderly, but doesn't offer breakdown by open heart / percutaneous (unlikely to have included PAVR)	
Cribier et al, 2002[32] Case study (first human implantation of Cribier-Edwards valve)	Wrong procedural technique – antegrade rather than retrograde approach	Balloon valvuloplasty was intended treatment for this patient (20mm; until pressure gradient reduced to 13mmHg and valve area increased to 1.06cm^2). However, deteriorating condition in week following led to first use of PAVR using mild sedation and local anaesthesia
Cribier et al, 2004[33] Case series	Wrong procedural technique – antegrade rather than retrograde approach	Case series. Six patients with severe calcific aortic stenosis and multiple comorbidities. Successful implantation in five, though three subsequently died of 'non-cardiac cause'. No residual pressure gradient, increased valve area, some

		regurgitation
Cribier et al, 2006[34]	Reject; results are duplicates of Cribier et al, 2006[21]	
Dalby et al, 2003[35]	Case series (4 patients): antegrade approach	
Eltchaninoff et al, 2006[36] Case series	Not a full report – abstract only	
Laborde et al, 2006[37]	Not a study. A narrative discussion of the technology	
Murtuza et al, 2008[38]	Irrelevant meta-analysis; not limited to percutaneous procedures – i.e. discusses minimal access aortic valve replacement	
Pai et al, 2007[39]	Study assesses survival after surgical aortic valve replacement, not percutaneous	
Paniagua et al, 2005[40] Case study	Wrong device – study considers the Paniagua valve	Case study in 62 year old man with 'inoperable calcific aortic stenosis' using retrograde approach and predilation with 18mm valvuloplasty balloon. Paniagua valve is balloon expandable and can be inserted with an 11F or 16F introducer. It has been tested in animals. This case study was technically successful and valve area increased, transvalvular pressure gradient decreased, though LVEF remained poor. On the third day there was respiratory distress, and increase in systolic pressure. Patient died on day five after implantation after biventricular failure and refractory hypotension
Panigua et al, 2006[41]	Wrong device – study considers the Paniagua valve	Describes first retrograde transcatheter implantation of Paniagua valve. Uses 16F sheath following predilation with 18mm valvuloplasty balloon. Transvalvular

		pressure gradient reduced, cardiac output increased. Death followed on day fiveafter respiratory distress, biventricular failure and refractory hypotension
Quaden et al, 2007[42]	Irrelevant; in vitro study	
Wenaweser et al, 2007[43]	Not specifically about success of PAVR	Describes successful percutaneous valve replacement in 80 year old man who had prior surgical valve replacement for severe aortic valve stenosis. Procedure involved retrograde insertion via surgical cut down of right femoral artery
Webb et al, 2006[27] Case series	Presents 6 month results from a case series that is more fully reported by Webb et al, 2007[25]	
Zajarias, Eltchaninoff and Cribier, 2007[44]	Not specifically about success of PAVR	Describes successful coronary intervention following percutaneous aortic valve replacement in an 85 year old man
Zegdi et al, 2008[45]	Not a full report – comment/letter	
Zegdi et al, 2008[46]	Not a full report – images	

Section 3 - The Impact

3.1 Demand

Bazian has modelled the demand for percutaneous aortic valve replacements in the East Midlands SCG region[♣] and across England in current nonsurgical candidates aged over 75 years.

Sources suggest that up to one third of patients aged over 75 years old with severe aortic stenosis are not referred for surgery because of severe symptoms and comorbidities.[47] In light of this we assume that the number of open heart valve replacements performed in England in this age group represent 2/3 of the people for whom replacement is indicated. We also assume that the remaining one third of patients are candidates for PAVR.

On this basis, Bazian estimates that 50 patients aged over 75 years will be suitable for PAVR each year in the East Midlands SCG region. This amounts to 600 cases across the whole of England. This demand will be shared between providers in the North and South.

If in future PAVR is also extended to those who are currently offered open surgery, then our model suggests that 1,800 people over 75 years will be candidates for PAVR each year across England. 155 of them will be from the East Midlands SCG region. We believe it unlikely that there will be calls to extend PAVR to such a broad population in the short to medium term.

These estimates are based on the following calculation:

Total number of >75 year olds living in England (mid 2006): **3,914,500**.[48]
Number of >75 year olds living in the East Midlands SCG (mid 2006): **339,000**.[48]
Number of aortic valve replacements[♠] in >75 year olds in 2005/2006: **1,194**.[49]

Based on the assumption that the current number of surgical procedures being performed in this age group represents 2/3 of the total in whom replacement is indicated,[♦] the true number needing aortic valve replacement in England is 1194 x 3/2 = **1,791**. This represents 0.046% (1791/3914500) of 75 year olds in England.

♣ includes the following PCOs: Bassetlaw, Derby City, Derbyshire County, Leicester City, Leicestershire County and Rutland, Lincolnshire, Northamptonshire, Nottingham City, Nottinghamshire County
♠ includes finished consultations for codes K26.1 (allograft replacement of aortic valve), K26.2 (xenograft replacement of aortic valve), K26.3 (prosthetic replacement of aortic valve), K26.4 (replacement of aortic valve not elsewhere classified) and assumes that the overwhelming majority of these (in this age group) will be for aortic stenosis
♦ based on EuroHeart Survey which suggest that 32% of patients with severe, symptomatic single valve disease do not undergo intervention[2,47]).

If PAVR is only offered to current nonsurgical candidates (i.e. one third of 1791), 597 patients aged over 75 are suitable for PAVR in England each year.

339,000 of England's 3,914,500 over 75 year olds live in the East Midlands meaning that there are about 51 current nonsurgical candidates in the East Midlands SCG region who are suitable for PAVR.

If the indication is also extended to those who are current surgical candidates, all 1,791 patients over 75 years are potential candidates for PAVR across England each year. 155 of them will come from the East Midlands SCG region. This estimates the maximum demand for the procedure if used in all adults who require valve replacement. PAVR is unlikely to be used in this way in the medium term.

3.2 Economics

3.2.1 Cost effectiveness

We found no published studies or models that have assessed the cost effectiveness of this procedure.

3.2.2 Cost

We have modelled the annual cost of the procedure in the SCG, based on the estimated number of candidates who may be suitable for the procedure. Caveats apply due to the assumptions we have made in our calculations (see section 3.3).

In the East Midlands SCG region, it will cost approximately £900,000 per annum to meet the demand for PAVR in current nonsurgical candidates over 75 years old. This is based on an approximate cost of £18,000 for the procedure: valve (£11,750), catheter lab team and non-pay costs (£3,188), CHDU costs (one day at £738), and stay on cardiology ward (five days at £375/day).♠ Overall, costs will increase if referrals are accepted from outside the PCOs considered here, if patients come from the younger age groups (under 75) or if the indication is extended to those patients who are currently candidates for surgical valve replacement.

♠ Costs are based on those presented in University Hospitals of Leicester business case, not including cost of pacemaker. The Brompton business case yields a similar overall figure (c£18k), although distribution of costs (associated with in-patient recovery) is somewhat different. It is unclear what 'non-pay costs' include for the catheter lab. Studies indicate that non-pay costs could include general anaesthesia, fluoroscopy, TEE.

Acute sector savings, associated with reduced admissions for complications, may offset some of the cost. From a societal and broader healthcare perspective, there may be savings in the costs of long term medical and social care for this severely disabled elderly patient group. However, we found no data to enable us to estimate the magnitude of such savings.

If the indication were extended to all patients requiring aortic valve replacement, then demand and cost would be three times as high (i.e. 155 patients in East Midlands each year at an annual cost of £2.8 million). Due to the paucity of data about treating this population with PAVR, the direct and offset costs are unclear. Importantly, extension to this wider group is likely to be very gradual so this estimate represents a theoretical maximum that is unlikely to be attained in the foreseeable future.

3.3 Caveats and sensitivities

3.3.1 Caveats

- The estimates are based on data for patients aged over 75 years only. We limited our calculations to this age group for the following reasons; nonsurgical candidates are more likely to be from older groups, there is good data from HES, NSO and EuroHeart Survey on aortic valve replacements, population size and referral patterns in this age group, aortic stenosis is more common in people aged over 75 than in the under 75s, patients over 75 are more likely to require valve replacement for a diagnosis of aortic stenosis (younger patients might require replacements for other conditions).
- As hospital episode statistics (from where we take data on number of AVRs per year) do not distinguish between indications, our model assumes that all valve replacements in the over 75 age group are performed for severe, symptomatic aortic stenosis and not for other conditions. As rheumatic stenosis is uncommon and congenital replacements are more usually performed in younger age groups, this assumption is likely to hold, though we could find no data to confirm this.
- Based on findings from the EuroHeart Survey,[2,47] we have assumed that referral patterns in England (and in East Midlands) are similar to those in Europe, i.e. that the number receiving surgical valve replacement for severe symptomatic aortic stenosis represents two thirds of the true number who need them.
- We have assumed that the remaining one third of people who are not receiving surgery could be offered PAVR. Therefore the model does not account for the patients in this

group who will be unsuitable for percutaneous procedures for practical reasons (e.g. because of atherosclerotic arteries).

- In the model we have assumed that the prevalence of surgical aortic valve replacement at a national level reflects the pattern in East Midlands.
- The demand for any treatment depends on the underlying prevalence of the condition. By basing our calculations on figures from one year (2005/2006) the model does not account for changes in the prevalence of aortic stenosis over time. Similarly, it assumes a fixed population of over 75 year olds in England and in East Midlands based on 2006 data from the national statistics office.
- The demand and cost estimates for the East Midlands region apply to the following PCOs: Bassetlaw, Derby City, Derbyshire County, Leicester City, Leicestershire County and Rutland, Lincolnshire, Northamptonshire, Nottingham City, Nottinghamshire County. Referrals from outside of these areas will alter the figures.
- The costs do not take into account those associated with managing procedure-related complications.

3.3.2 Sensitivities:

- Demand and cost figures will rise if referrals for PAVR come from the younger age groups (under 75 year olds).
- If a significant proportion of the total aortic valve replacements performed in the over 75s (data from hospital episode statistics) are for indications other than aortic stenosis, this reduces the demand in this age group, thereby reducing the demand and cost estimates.
- Demand for the procedure and associated costs will reduce if nonsurgical candidates turn out to be unsuitable for PAVR on practical (e.g. anatomical) grounds.
- The estimates are sensitive to the number of people in the denominator. Cost and demand will increase in response to increasing numbers of people at risk (i.e. growing population of over 75 year olds). It is reasonable to assume that with the ageing population, the demand for treatments for aortic stenosis will increase, though this assumes a fixed incidence rate.

Section 4 - Appendix

4.1 Methods

4.1.1 Purpose and overview of reports

This evidence report is designed to examine the evidence regarding clinical and cost-effectiveness of percutaneous aortic valve replacement (PAVR) for severe aortic stenosis to inform local policy. Research has been identified, sourced, appraised, analysed and summarised by senior medical and scientific evidologists. The briefing has been edited for plain English and checked for validity.

4.1.2 Search and appraisal

An experienced evidology informaticist searched a range of databases and guideline sites (see table 1) in order to find articles of any study type relevant to PAVR. Search strings, including key words and sensitivity/specificity filters, are stored and available to users on request; the major search terms used (keywords and indexing terms) are shown in table 2. Studies in languages other than English were not included. All references are stored using the Reference Manager™ bibliographic software.

The initial search found a total of 940 articles. The first pass appraisal of these articles selected a total of 96 articles (for background relevance and potential studies) to proceed for further appraisal. Of these, a second appraisal resulted in 34 studies being identified to source and analyse at full text. Finally, after appraising these 34 full text articles, a total of 14 studies were selected for inclusion in the review (for details of appraisal criteria used see table 3). 13 other articles were included for background reference.

Table 1: Sources of literature for Bazian Briefings

Databases	MEDLINE EMBASE Cochrane Central Register of Controlled Trials Cochrane Database of systematic reviews Health Technology Assessment Databases NHS Economic Evaluation Database Database of Abstracts of Reviews of Effectiveness (DARE) EuroINTERVENTION (The Official Journal of the EuroPCR and the European Association of Percutaneous Cardiovascular Interventions – EAPCI)
Guidelines	National Library of Guidelines National Guidelines Clearinghouse NZ Guidelines Group ASERNIP-S

	Australian NHMRC CMA Infobase Guidelines International Network

Table 2: Search terms (keywords and thesaurus headings) used

	Intervention	Condition
Keywords	PAVI OR PAVR OR TAVI OR TAVR OR CoreValve OR Edwards sapien OR (percutan* OR transcathet* OR translumin* OR endovasc*) NEAR valve*	(Aort* OR heart) AND valve
Medline Thesaurus terms	Heart Valve Prosthesis OR Heart Valve Prosthesis Implantation	Heart Valve Diseases OR Aortic Valve OR Aortic Valve Stenosis
Embase Thesaurus terms	Heart Valve Prosthesis OR Heart Valve Prosthesis Implantation OR Aorta Valve Prosthesis OR Heart Valve Replacement OR Aorta Valve Replacement	Heart Valve Diseases OR Aortic Valve OR Aortic Valve Stenosis OR Aorta Valve Disease OR Aorta Stenosis/

Table 3: Appraisal criteria

	First appraisal (title and abstracts)	Second appraisal (abstracts)	Third appraisal (full texts)	Included*
Publication	Any	Studies (case studies, case series, cohorts, non-randomised trials, RCTs)	Studies (case studies, case series, cohorts, non-randomised trials, RCTs)	Studies (case studies, case series, cohorts, non-randomised trials, RCTs)
Population	Aortic stenosis	Aortic stenosis	Severe, symptomatic aortic stenosis	Severe, symptomatic aortic stenosis
Intervention	Percutaenous or minimally invasive procedures for aortic valve replacement	Percutaneous procedures for aortic valve replacement	Percutaneous retrograde aortic valve replacements with CoreValve or Edwards valve	Percutaneous retrograde aortic valve replacements with CoreValve or Edwards valve
Comparator	Any	Any	Any	Any
Outcome	Any	Any	Any	Any

* Table does not include appraisal criteria for publications that were included for background reference only.

4.1.3 Critical appraisal methodology

Bazian uses recognised approaches to appraise studies for inclusion in systematic reviews. In the case of emerging technologies such as percutaneous aortic valve replacements, randomised controlled trials, that we would normally favour for efficacy questions are unavailable. For this reason we did not exclude studies on the basis of their design.

Retrieved articles underwent a three stage appraisal:

- The first appraisal was conducted by an experienced evidology informaticist who applied broad inclusion criteria to all the articles retrieved by the search. Articles that were clearly irrelevant to the review question were excluded at this stage. Exclusion criteria: non-human studies, studies in the wrong population (e.g. replacements for congenital disease), percutaneous replacements for other valves (i.e. not aortic), studies solely of surgical valve replacements, studies of vascular procedures that are clearly not percutaneous, studies of percutaneous procedures that are not valve replacements, non English language articles.
- An experienced scientific evidology analyst undertook the second appraisal – again at the level of the study abstract, looking in greater depth for:
    - *Relevance of study to the question*: Studies were only included if they were in patients with aortic stenosis, and used a retrograde percutaneous procedure, with either the Edwards or the CoreValve device. Studies were not excluded on the basis of comparators or outcomes in order to maximise sensitivity.
    - *Validity of research design:* As high quality evidence was not available, we included lower level evidence of efficacy (e.g. observational studies, case series and case reports). We clearly describe any caveats associated with conclusions and recommendations that are based on these suboptimal study designs.
- Full texts are retrieved for all articles deemed relevant at this stage and for those where more information is needed to make a decision. The third appraisal is based on full texts, using the same criteria as for second appraisal.

4.1.4 Synthesis of studies

Data from the included studies were extracted into tables. In the absence of measures of effect from randomised controlled studies, the results were synthesised narratively rather than by meta-analysis. We discuss whether these results can help answer the policy question, and the implications of the evidence gaps.

4.1.5 Writing up the report

This report was overseen, checked and signed off by Dr Rob Cook who leads the scientific team. Dr Cook is ultimately responsible for all aspects of quality assurance for this project. A scientific evidology analyst wrote the first draft and a clinical analyst checked the accuracy of the data and their interpretation. Other members of the evidology team independently proof read the document to check for sense.

4.1.6 Who is involved in Bazian's reports?

Bazian's scientific team comprises informaticists, scientists, clinicians and editors, all of whom have advanced training in systematic reviewing and policy briefing. All contributors' work is formally assessed and continuously monitored. Further details regarding the team and their experience is available at www.bazian.com.

4.2 Terms of use

This report has been produced by Bazian Ltd for the East Midlands Specialist Commissioning Group. It is to be used only for, or in connection with, the purposes of the SCG, and must not be accessed, distributed or copied for any other purpose. While Bazian Ltd has taken care in the preparation of this assessment, we do not make any warranty as to its content or will be liable to any person relying on or using it for any purpose.

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