NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedures overview of aortic valve reconstruction with processed bovine pericardium

The aortic valve (1 of 4 valves in the heart) sometimes becomes leaky or narrow. This means the blood doesn't get pumped around the body properly, which can cause palpitations, fatigue, shortness of breath and chest pain. In this procedure, chemically treated cow pericardium (the tissue around the heart) is used to make a new valve to replace the damaged aortic valve in the patient. The aim is to improve the patient's symptoms.

Contents

Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedures overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the

medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in July 2017 and reviewed in November 2017

Procedure name

- Aortic valve reconstruction with processed bovine pericardium

Specialist societies

- Society for Cardiothoracic Surgery of Great Britain and Ireland
- British Cardiovascular Society

Description of the procedure

Indications and current treatment

Aortic valve disease (stenosis or regurgitation) is usually progressive, causing an increase in cardiac workload, left ventricular hypertrophy and heart failure. Symptoms can include palpitations, fatigue, shortness of breath and chest pain on exertion. Mortality rates are high in symptomatic patients.

Conventional treatment for a significantly diseased aortic valve is surgical replacement with an artificial (biological or mechanical) prosthesis. Transcatheter aortic valve implantation (TAVI) may also be considered. Bioprosthetic valves do not perform as well as native valves and have limited durability, which may be an issue for younger patients. At present, lifelong anticoagulation is required in patients with mechanical valves. This increases the risk of haemorrhagic complications and is not optimal in women wishing to become pregnant.

In some patients with aortic regurgitation the aortic valve may be repaired with patches as an alternative to replacement.

Aortic valve reconstruction with bovine pericardium may be considered in patients who cannot or refuse to take anticoagulation, patients with an aorta too narrow for a standard prosthetic valve and young patients who wish to avoid long-term anticoagulation.

What the procedure involves

Under general anaesthesia, access to the heart is achieved by a sternotomy and the patient is established on cardiopulmonary-bypass. The heart is stopped with cardioplegic arrest. The aorta is opened and the valve is inspected. The diseased valve cusps are carefully removed. The intercommissural distances are measured, and commercially available bovine pericardium is trimmed exactly to the desired size using a template, and sutured to the annulus to replace the removed cusp(s). The aorta is closed, normal circulation is restored and the chest is closed. The function of the valve is assessed intraoperatively by transoesophageal echocardiography.

Outcome measures

New York Heart Association (NYHA) heart failure classification

Class	Symptoms
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity, e.g. no shortness of breath when walking, climbing stairs etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.

Recommendations for classification of aortic stenosis, European Society of Cardiology and American Society of Echocardiography

Severity	Aortic sclerosis	Mild	Moderate	Severe
Aortic jet velocity (m/s)	≤2.5 m/s	2.6–2.9	3.0–4.0	>4.0
Mean gradient (mmHg)	—	<20 (<30[a])	20–40[b] (30–50[a])	>40[b] (>50[a])
Aortic valve area (AVA, cm^2)	—	>1.5	1.0–1.5	<1.0
Indexed AVA (cm^2/m^2)		>0.85	0.60–0.85	<0.6
Velocity ratio		>0.50	0.25–0.50	<0.25

[a]European Society of Cardiology
[b]American Heart Association and American College of Cardiology guidelines

Classifications for aortic regurgitation of the British Society of Echocardiography

Severity	Mild	Moderate	Severe
Vena contracta width (cm)	<0.3		>0.6
Jet width/left ventricle outflow tract (LVOT) diameter (%)	<25		≥65
Regurgitant volume (ml/beat)	<30	31–59	≥60
Regurgitant fraction (%)	<30	31–49	≥50
Regurgitant orifice area (cm^2)	<0.1	0.11–0.29	≥0.3
VTI diastolic flow reversal (upper descending aorta, cm)			15
Pressure half time (ms)	>500		<250

Efficacy summary

Survival

In a case series of 92 patients treated by aortic valve reconstruction (AVR), survival was 89% (24/27) using bovine pericardium at a mean follow-up of 12 years, and 91% (59/65) using autologous pericardium at a mean follow-up of 10 years[1, 2].

In a case series of 135 patients treated by AVR using glutaraldehyde-treated bovine pericardium, 5-year cumulative survival was 98% (133/135). One death occurred at re-operation and 1 death was due to duodenal cancer[3].

In a case series of 3 paediatric patients treated by AVR using glutaraldehyde-treated bovine pericardium, there were no deaths at a range of 8 to 10 months follow-up[4].

In the case series of 135 patients treated by AVR, 5-year event-free survival was 88% (119/135)[3].

Re-operation

In the case series of 92 patients, freedom from re-operation was 48% in the bovine pericardium group at a follow-up of 16 years. Causes of re-operation in the bovine pericardium group were structural valve degeneration (11/27), endocarditis (1/27) and other (2/27)[1, 2].

In the case series of 135 patients, 5-year freedom from re-operation was 93% (125/135). Two re-operations were due to detached pericardial leaflet causing severe regurgitation (addressed with repeat suturing), and 4 were due to

endocarditis (of which 1 was addressed with repeat AVR and 3 with bioprosthetic valve replacement)[3].

Technical failure

In the case series of 92 patients, technical failure was reported in 15% (4/27) of patients in the bovine pericardium group (inappropriate size cusps)[1, 2].

Cardiopulmonary bypass time

In the case series of 92 patients, mean cardiopulmonary bypass time was 150 (±33) minutes in the bovine pericardium group and 129 (±25) minutes in the autologous pericardium group[1,2].

In the case series of 135 patients, mean cardiopulmonary bypass time was 178 (±31) minutes[3].

Aortic cross-clamp time

In the case series of 92 patients, mean aortic cross-clamp time was 100 (±20) minutes in the bovine pericardium group and 95 (±20) minutes in the autologous pericardium group[1,2].

In the case series of 135 patients, mean aortic cross-clamp time was 112 (±19) minutes[3].

Aortic valve pressure gradient

In the case series of 135 patients, the mean aortic valve pressure gradient was 9.6 ± 4.3 mmHg in the group treated with a 3-leaflet technique, and 14.1 ± 4.1 mmHg in the group treated with a 2-leaflet technique, at 1 year follow-up[3].

Aortic valve function

In the case series of 92 patients treated by AVR who didn't have re-operation, aortic valve function was reported as good (5/7) and mildly impaired (2/7) in the patients in the bovine pericardium group, and as good (46% [13/28]), mildly impaired (29% [8/28]), moderately impaired (21% [6/28]) and severely impaired (1/28) in the autologous pericardium group, at 16-years follow-up[1, 2].

In the case series of 135 patients, 71% (96/135) of patients had no aortic regurgitation, 22% (30/135) had trivial regurgitation, 5% (7/135) had mild regurgitation and 2% (2/135) had moderate regurgitation, at hospital discharge[3].

Safety summary

Death

No in-hospital deaths from cardiac causes were reported in the patients treated by AVR using bovine pericardium in a case series of 92 patients, compared with 3% (2/65) of patients treated by AVR using autologous pericardium. Late deaths from cardiac causes were reported in 4% (1/27) of patients in the bovine pericardium group and 3% (2/65) of the patients in the autologous pericardium group in the same case series. Death at reoperation was reported in 7% (2/27) of patients in the bovine pericardium group and 2% (1/65) of patients in the autologous pericardium group, also in the case series of 92 patients[1, 2].

No in-hospital deaths from cardiac causes occurred in patients treated with AVR with bovine pericardium in a case series of 135 patients[3].

In-hospital events

In-hospital events were reported in 9% (12/135) of patients treated with AVR with bovine pericardium in the case series of 135 patients. These events were transient ischemic attack (2%; 2/135), cerebral infarction (2%; 2/135), pericardial tamponade caused by pericardial effusion requiring catheter drainage (2%; 3/135) and repeat exploration due to postoperative bleeding (4%; 5/135)[3].

Cusp calcification

Cusp calcification was reported in 3/7 patients undergoing AVR using bovine pericardium and 1/28 patients undergoing AVR using autologous pericardium in the case series of 92 patients[1, 2].

Endocarditis

Endocarditis leading to re-operation was reported in 4% (1/27) of patients undergoing AVR with bovine pericardium and 11% (7/65) of patients undergoing AVR using autologous pericardium in the case series of 92 patients[1, 2].

Endocarditis leading to re-operation was reported in 3% (4/135) of patients in the case series of 135 patients treated by AVR with bovine pericardium[3].

Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, specialist advisers are asked about anecdotal adverse events (events which they have heard about) and about theoretical adverse events (events which they think might possibly occur, even if they have never happened). For this procedure, specialist advisers listed no anecdotal adverse events. They considered that the following were theoretical

adverse events: residual aortic regurgitation, impaired short/mid/long-term durability and early valve failure.

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to aortic valve reconstruction with processed bovine pericardium. The following databases were searched, covering the period from their start to July 2017: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

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

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with aortic valve disease, including stenosis or regurgitation with or without infective endocarditis.
Intervention/test	Aortic valve reconstruction.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on 193 patients from 4 case series[1, 2, 3, 5] and 1 case report[4].

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

Table 2 Summary of key efficacy and safety findings on aortic valve reconstruction with processed bovine pericardium

Studies 1 and 2 Halees Z A (2005) and Duran CMG (1998)

Details

Study type	**Case Series**
Country	Saudi Arabia
Recruitment period	1988 to 1995
Study population and number	n=**92**, AVR treated with bovine pericardium (Group I, the first 27 patients) or glutaraldehyde treated autologous pericardium (Group II, the following 65 patients)
Age and sex	Group I (bovine) – Mean 21.2 (12-36) years, 67% (18/27) males Group II (autologous) - Mean 33.3 (12-68) years, 72% (47/65) males
Patient selection criteria	Patients requiring surgery to treat aortic stenosis, regurgitation or mixed aortic disease. Mitral valve replacement with a mechanical prosthesis was considered a contraindication.
Technique	The pericardium was trimmed and shaped to the normal aortic valve and to a size corresponding to the patient's aortic annulus as determined by transoesophageal echocardiography. The aortic cusps were excised. With experience the technique evolved towards total excision of the aortic valve, including those heavily calcified where no cusp remnant was left. Pre and post-operative cardiac function were assessed using a transoesophageal echocardiograph.
Follow-up	**Mean 10.5 (9 to 16) years**
Conflict of interest/source of funding	Not reported

Analysis

Follow-up issues: Seven patients were lost to follow-up, 3 from group I and 4 from group II. The mean follow-up was longer for group I patients (12 versus 10 years).

Study design issues: The initial surgical technique was to repair the valve with a strip of commercially available glutaraldehyde-treated bovine pericardium. The strip was three times longer than the diameter of the aortic orifice plus 2 cm and one third as high as the total length. One of its lengths was trimmed into 3 curves, leaving a "commissural" area of at least 1 cm. Four patients treated by this technique early in the series did not have satisfactory results and were not included in the analysis. A replacement with prosthetic valve was done alternatively with no mortality. One patient had an emergency aortic valve replacement after successful AVR. This was required because of ischaemic changes in the left coronary artery territory caused by obstruction of the left coronary ostium. The pericardial cusps were too high and redundant and, during diastole, would bend the free margin towards the Valsalva sinus, possibly causing obstruction of the coronary ostiae. This patient was also not included in the analysis.

There is no assessment of post-surgical exercise tolerance or quality-of-life outcomes.

Study population issues: In the autologous pericardium group 18% (12/65) of patients had degenerative aortic valve disease, compared to none in group I. This difference was statistically significantly different between groups (p=0.005).

83% of patients had rheumatic aetiology.

Patients were routinely placed on aspirin 100 mg once per day. 9 patients received anticoagulation with warfarin.

Other issues: The papers by Halees (2005) and Duran (1998) report data from the same sample. Both papers are included in table 2 because the description of the safety and efficacy outcomes and surgical technique description are complementary.

Key efficacy and safety findings

Efficacy

n=92 (27 bovine pericardium , 65 autologous pericardium)

	Group I (bovine) n=27	Groups II (autologous) n=65
Mean cardiopulmonary bypass time (min)	150 (±33)	129 (±25)
Mean aortic cross-clamp time (min)	100 (±20)	95 (±20)
Technical failure	15% (4/27)	-
Survival (at last follow-up)[1]	89% (24/27)[2]	91% (59/65)[3]
Freedom from reoperation (10 years)	68%	72%[4]
Freedom from reoperation (16 years)	48%	45%[4]
Freedom from SVD (10 years)	78%	80%
Freedom from SVD (16 years)	55%	58%
Aortic valve function (16 years)[5]		
Aortic valve impairment	**n=7**	**n=28**
Good	5/7	46 % (13/28)
Mild	2/7	29% (8/28)
Moderate	-	21% (6/28)
Severe	-	1/28
Re-operation (all causes)	52% (14/27)	42% (27/65)
Re-operation for SVD	41% (11/27)	26% (17/65)
Re-operation caused by endocarditis	4% (1/27)	11% (7/65)
Re-operation for other reasons	7% (2/27)	5% (3/65)
Pericardial cusps calcification[6]	3/7	1/28[7]

Excluding patients who needed reoperation, 90% of the survivors (both groups) are asymptomatic in NYHA-FC I–II.

[1]Mean follow-up was 12 years for Group I and 10 years for Group II

[2]One late cardiac death and two deaths at re-operation.

[3]Two in-hospital deaths (1 patient died of myocardial failure and low cardiac output and the other from haemorrhage due to coronary sinus rupture); 3 late deaths (2 cardiac and 1 car accident); 1 death at re-operation.

[4]One patient had the reconstructed aortic valve replaced at day 5 because of aortic regurgitation. This was probably related to a dilated aortic annulus. One patient had reoperation because of commissural tearing 8 months after AVR.

[5]At 16 years follow-up, 7 patients remain free of reoperation in group I and 28 in group II.

[6]At 16 years follow-up, prevalence reported in patients that were free of reoperation.

[7]Reported in 1 patient with severe disease. This information was not reported for patients with mild and moderate aortic disease.

Safety

	Group I	Group II
In hospital deaths	0	3% (2/65)[1]

[1]One patient died of myocardial failure and low cardiac output and the other from haemorrhage due to coronary sinus rupture.

Abbreviations used: Aortic valve reconstruction, AVR; SVD, structural valve degeneration; NYHA-FC, New York Heart Association (NYHA) Functional Classification (I= no limitation, II= slight limitation on physical activity, III= marked limitation on physical activity, IV= unable to carry on any physical activity without discomfort).

Study 3 Song MG (2014)

Details

Study type	**Case Series**
Country	South Korea
Recruitment period	2007-2013
Study population and number	n=**135** bicuspid valve disease patients having aortic valve reconstruction surgery with bovine pericardium.
Age and sex	Mean 49.2 (20-80) years; 73% (99/135) male
Patient selection criteria	Included bicuspid valve only, with or without raphe, presenting with stenosis aortic regurgitation or stenotic insufficiency Excluded concomitant mitral valve surgery, or surgery for acute aortic dissection.
Technique	Aortic valve reconstruction surgery, using either 2- leaflet (n=13) or 3- leaflet technique (n=122) Aortic valves were fully excised and replaced with new leaflets made from bovine pericardium. Dilated aortic annuli were reduced by plication of the fibrous portion with use of nonexpendable inner and outer annulus strips (ScienCity, South Korea). New commissures and leaflets were made using glutaraldehyde-treated bovine pericardium (Supple Periguard, Synovis, USA), according to measurement of the diameter of sinotubular junction, using the C-Leafcon template (ScienCity, South Korea). All 3 leaflets were identical in size (22-30mm).
Follow-up	**Mean 2.8 (0.2-5.5) years**
Conflict of interest/source of funding	Not reported

Analysis

Follow-up issues: 100% follow-up is reported. 112 patients were monitored for 1 year or longer.

Study design issues: Initially the 2 leaflet technique was used, in the first 13 patients, however these were observed to have significantly high valve pressure gradients. The procedure was subsequently switched to a 3-leaflet technique (n=122).

There is no assessment of post-surgical exercise tolerance or quality-of-life outcomes.

Study population issues: Concomitant aortic wrapping with an artificial graft in 47% of patients and concomitant septal myectomy in 10%. There were 75% (SD 55.6) of patients with aortic stenosis, 54% (SD 40) with regurgitation and 6% (SD 4.4) with stenotic insufficiency. Preoperative left ventricular ejection fraction was 0.65 (SD 0.1).

Other issues: South Korea setting and population may not be fully generalizable to UK.

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>

n= 135 patients

Procedural results:

Mean cardiopulmonary bypass time (min)	178 (±31)
Mean aortic cross-clamp time (min)	112 (±19)
Post-operative echocardiogram:	
No aortic regurgitation	93% (126/135)
mild to moderate regurgitation	7% (9/135)

Long-term efficacy:

Cumulative survival (5 year)	98%[1]
Event-free survival (5 year)	88% (119/135)[2]
Freedom from reoperation (5 year)	93% (125/135)[3]

Valve pressure gradients:

Follow up at latest available ECG (at least 1 year):

	3-leaflet technique (n=99)	**2-leaflet technique (n=13)**
Peak Pressure Gradient (mmHg)	18.2 ± 7.1	25.5 ± 6.4
Mean Pressure Gradient (mmHg)	9.6 ± 4.3	14.1 ± 4.1

At hospital discharge 71% (96/135) patients had no aortic regurgitation, 22% (30/135) had trivial, 5% (7/135) had mild and 2% (2/135) had moderate.

[1]Two deaths: 1 death following re-operation, 1 due to duodenal cancer.

[2]Two late cerebral infarctions, 12 in-hospital events (as shown in safety column).

[3]Re-operations: 6 (4.3%), 2 due to detached pericardial leaflet causing severe regurgitation (addressed with repeat suturing), and 4 due to endocarditis (of which 1 addressed with repeat AVR and 3 with bioprosthetic valve).

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In-hospital events:

Deaths: 0

TIA: 2% (2/135)

Cerebral infarction: 2% (2/135)

Pericardial tamponade caused by pericardial effusion, requiring catheter drainage: 2% (3/135)

Repeat exploration due to postoperative bleeding: 4% (5/135)

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<tr><td colspan="2">Abbreviations used: AVR, aortic valve reconstruction, SD, standard deviation TIA, transient ischemic attack</td></tr>
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Study 4 Kim KH (2014)

Details

Study type	**Case Report**
Country	South Korea
Recruitment period	2007
Study population and number	n=**1,** AVR treated with bovine pericardium
Age and sex	64 years, male.
Patient selection criteria	Not reported
Technique	Aortic valve fully excised and replaced with new leaflets made from bovine pericardium. Dilated aortic annulus was reduced by plication of the fibrous portion with use of nonexpendable inner (Dacron, flexible but inelastic) and outer (thicker and softer than inner ring) annulus rings (ScienCity, South Korea). New commissures and leaflets were made using bovine pericardium (Supple Periguard, Synovis, USA), according to measurement of the diameter of sinotubular junction, using the C-Leafcon template (ScienCity, South Korea).
Follow-up	**5.5 years**
Conflict of interest/source of funding	Not reported

Analysis

Follow-up issues:

Study design issues: Initially planned to insert porcine replacement valve but aortic annulus was found to be too small (19mm).

Study population issues:

Other issues: Likely that this patient is already included in the study by Song (2014).

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: 1 At 5.5 years: **Coaptation height** 7 mm **Mean pressure gradient annular** 2 mmHg **Mean pressure gradient STJ** 17 mmHg	No safety events reported at 5.5 years.
Abbreviations used: AVR, aortic valve reconstruction; STJ, Sinotubular junction.	

Study 5 Mazzitelli D (2015)

Details

Study type	**Case Series**
Country	Germany
Recruitment period	Not reported
Study population and number	n=**3,** AVR treated with bovine pericardium
Age and sex	Range 5-15 years; 2/3 male
Patient selection criteria	Not reported 2 unicuspid, one bicuspid. All with leaflet dysplasia causing heart dysfunction.
Technique	Ozaki procedure. The diseased valve cusp(s) is carefully removed. The intercommissure distances are measured using Ozaki sizers and commercially available bovine pericardium is trimmed to the desired size and stitched to the annulus to replace the removed cusp(s). CardioCel (Admedus, Australia) bovine pericardium was used. The material is decellularised, and cross-linked using a low-concentration glutaraldehyde solution, and a proprietary anti-calcification process.
Follow-up	**Range 8-10 months**
Conflict of interest/source of funding	Financial relationship, with Admedus, makers of the CardioCel bovine pericardium material.

Analysis

Follow-up issues:

Study design issues: Financial relationship with bovine pericardium material maker.

Study population issues: There were 2 patients with unicuspid and 1 with bicuspid valve.

In 1 patient, leaflet shaving for cusp extension was initially attempted but failed, then procedure changed to full leaflet excision and reconstruction.

Other issues:

Key efficacy and safety findings

Efficacy	Safety
n=3 Post-operative echocardiogram assessment showed technical success in all 3 patients. This was assessed by good leaflet coaptation height, good leaflet opening, and no residual regurgitation. At 8-10 months, no re-operation or deaths. Mild regurgitation reported in 1 patient.	At 8-10 months, no safety events
Abbreviations used: AVR, aortic valve reconstruction.	

Validity and generalisability of the studies

- Aortic valve reconstruction is novel and therefore the available evidence is limited.
- Limitations of the evidence are: limited number of studies, small number of patients, no randomised data, limited efficacy and safety reporting.
- Different bovine pericardium materials were used in these studies.
- There was variability in the procedure technique used in these studies.

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

Related NICE guidance

Below is a list of NICE guidance related to this procedure.

Interventional procedures

- Transcatheter valve-in-valve implantation for aortic bioprosthetic valve dysfunction. NICE interventional procedures guidance 504 (2014). Available from www.nice.org.uk/guidance/IPG504
- Transcatheter aortic valve implantation for aortic stenosis. NICE interventional procedures guidance 421 (2012). Available from www.nice.org.uk/guidance/IPG421
- Percutaneous fetal balloon valvuloplasty for aortic stenosis. NICE interventional procedures guidance 175 (2006). Available from www.nice.org.uk/guidance/IPG175
- Balloon valvuloplasty for aortic valve stenosis in adults and children. NICE interventional procedures guidance 78 (2004). Available from www.nice.org.uk/guidance/IPG78

Additional information considered by IPAC

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by Specialist Advisers, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. Two Specialist Advisor Questionnaires for aortic valve reconstruction with processed bovine pericardium were submitted and can be found on the NICE website [update HYPER LINK with IP number AND THEN to http://www.nice.org.uk/guidance/ipgXXX/evidence with IPG number on publication].

Patient commentators' opinions

Commentary from 1 patient who had experience of this procedure was received, which was discussed by the committee.

Company engagement

A structured information request was sent to 2 companies who manufacture a potentially relevant device for use in this procedure. NICE received 2 completed submissions. These were considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

Issues for consideration by IPAC

- The use of glutaraldehyde for the purpose of intraoperative autologous pericardium treatment is not regulated in the UK.
- This procedure might be of particular interest to a particular patient group.

References

1. Halees ZA, Shahid MA, Sanei AA et al. (2005) Up to 16 years follow-up of aortic valve reconstruction with pericardium: A stentless readily available cheap valve? European Journal of Cardio-thoracic Surgery 28: 200-205.
2. Duran CMG, Gometza B, Shahid M et al. (1998) Treated bovine and autologous pericardium for aortic valve reconstruction. Annals of Thoracic Surgery 66: 166-169.
3. Song M G, Yang H S, Choi J B, Shin J K, Chee H K, and Kim J S (2014) Aortic valve reconstruction with use of pericardial leaflets in adults with bicuspid aortic valve disease: early and midterm outcomes. Texas Heart Institute Journal 41(6), 585-91.
4. Kim K H, Choi J B, Kim M H, Kim W H, Lee M K, and Lee S Y (2014) Aortic valve leaflet replacement with bovine pericardium to preserve native dynamic capabilities of the aortic annulus. Texas Heart Institute Journal 41(1), 97-9.
5. Mazzitelli D, Nobauer C, Rankin J S, Vogt M, Lange R, and Schreiber C (2015) Complete aortic valve cusp replacement in the pediatric population using tissue-engineered Bovine pericardium. Annals of Thoracic Surgery 100(5), 1923-1925.

Additional relevant papers

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

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Bjornstad K, Duran RM, Nassau KG et al. (1996) Clinical and echocardiographic follow-up after aortic valve reconstruction with bovine or autologous pericardium. American heart journal 132: 1173-1178.	Case series n=86 FU=35 months	There were two in-hospital and three late deaths. Warfarin was not given, and no thromboembolic events occurred. Five (6%) patients needed reoperation because of severe aortic regurgitation. Peak aortic valve gradients remained low (26 +/- 14 mm Hg for the bovine group and 16 +/- 16 mm Hg for the autologous group). One patient is awaiting surgery for aortic stenosis after 76 months. Leaflet thickening at latest follow-up was marked in six (9%) patients. Left ventricular dimensions normalized postoperatively and showed only insignificant increase during follow-up. This technique is a promising alternative to valve prosthesis in selected patients; however, longer follow-up is necessary to assess long-term results.	Overlap with papers 1 and 2 in table 2.
Duran CM, Gometza B, Kumar N et al. (1995) Aortic valve replacement with freehand autologous pericardium. Journal of Thoracic & Cardiovascular Surgery 110: 511-516.	Case series n=51 FU= 21 months	There were no hospital and two late deaths. Three patients required reoperation because of failure of the pericardial valve as a result of infective endocarditis in two (5 and 31 months after operation) and commissural tear at 8 months in another. One patient underwent reoperation at 24 months because of failure of the mitral valve repair. The pericardial aortic valve, which had 2+ regurgitation since the first operation, was also replaced. Macroscopic and microscopic examination findings in the excised pericardium were excellent. No thromboembolic events have been detected and no patient received anticoagulation therapy except one after mitral valve reoperation and replacement with a mechanical valve. The actuarial survival was 84.53% +/- 12.29% at 60 months, freedom from failure of the aortic reconstruction 83.83% +/- 8.59%, and freedom from any event 72.59% +/- 12.79%. Doppler echocardiographic study at most recent follow-up showed a mean gradient of 12.56 +/- 8.10 mm Hg and mean regurgitation on a scale from 0	Overlap with papers 1 and 2 in table 2.

		to 4+ of 0.80 +/- 0.66. Although the maximum follow-up is only 5 years, the results obtained so far encourage us to continue replacing the aortic valve with stentless autologous pericardium.	
Duran C, Kumar N, Gometza B, al Halees, and Z (1991) Indications and limitations of aortic valve reconstruction. Annals of Thoracic Surgery 52, 447-53; discussion 453-4	Case series n=38 FU=up to 12 months	Two techniques were used: repair (annular and leaflet plasties, 69 cases) and cusp extension with glutaraldehyde-treated pericardium (25 bovine, 13 autologous). There were two hospital deaths (1.8%), both in the repair group, and no late deaths or embolic events. Only 5 patients (4.7%) were anticoagulated. In the repair group there were 12 reoperations, four (5.9%) due to aortic and eight to mitral dysfunction. In the cusp extension group there were two reoperations due to mitral dysfunction. Echocardiographic follow-up showed better results with cusp extension. In conclusion, conservative operation for aortic regurgitation is possible in a high percentage of young rheumatic patients and does not require anticoagulation. Cusp extension is more reliable than repair in terms of early results, although its long-term durability is not yet known.	Overlap with papers 1 and 2 in table 2.
Duran C M, and Gometza B (1994) Aortic valve reconstruction in the young. Journal of Cardiac Surgery 9, 204-8	Case series n=72 FU= up to 18 months	In 72 patients (mean age 27.7 years), a cusp extension was undertaken with glutaraldehyde treated bovine (27 pts) or autologous (45 pts) pericardium. In the "plasty" group, there were 8 (4%) hospital deaths and 8 (4.1%) late deaths with an actuarial survival of 86.05% +/- 3.97%. No thromboembolic events were detected in patients with isolated aortic surgery. There were 32 reoperations without mortality, 22 due to progressive rheumatic disruption of the mitral repair. There was severe aortic dysfunction in 17 (8.76%) cases. There was no hospital mortality among the 72 patients with cusp extensions. There were two (2.8%) late deaths and no thromboembolic events. No patient was anticoagulated. Four patients required reoperation on the aortic valve without mortality. The last echocardiographic follow-up showed stability of the reconstruction. These techniques offer a valid alternative to valve replacement in this difficult category of patients.	Overlap with papers 1 and 2 in table 2.
Duran C M, Gometza B, Kumar N, Gallo R, and Bjornstad K (1995) From aortic cusp extension to valve replacement with stentless pericardium. Annals	Case series n=82 FU=51 months	There were one in-hospital and three late deaths. No patient received anticoagulation, and no embolic events were detected. Nine patients required reoperation as a result of failure of mitral valve repair in 4 and severe aortic regurgitation in 5 (endocarditis [n = 2], commissural tear [n = 1], root dilation [n = 1], calcification of one bovine cusp [n = 1]	Overlap with papers 1 and 2 in table 2.

of Thoracic Surgery 60, S428-32		at 58 months). There were no reoperative deaths. Complete linear echocardiographic follow-up of these patients showed low gradients, valve competence, and no progressive deterioration. No difference between techniques was detected.	

Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	06/11/17	Issue 10 of 12, October 2017
HTA database (Cochrane Library)	06/11/2017	Issue 10 of 12, October 2017
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	06/11/17	Issue 10 of 12, October 2017
MEDLINE (Ovid)	06/11/17	1946 to October Week 4 2017
MEDLINE In-Process (Ovid)	06/11/17	November 03, 2017
EMBASE (Ovid)	06/11/17	1974 to 2017 Week 45
PubMed	06/11/17	n/a
BLIC	06/11/17	n/a

Trial sources searched 8th June 2016

- Clinicaltrials.gov
- ISRCTN
- WHO International Clinical Trials Registry

Websites searched 8th June 2016

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- EuroScan
- General internet search

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1 Heart Valve Diseases/ (23418)
2 Aortic Valve Insufficiency/ (14605)
3 Aortic Valve Stenosis/ (23186)
4 ((aortic* or cardi* or heart*) adj4 (insufficient* or stenos* or incompetenc* or regurgitat* or disease* or aneurysm)).tw. (357971)
5 (pancarditis adj4 endocarditis).tw. (6)
6 Rheumatic Diseases/eh (81)
7 or/1-6 (387486)
8 ((bovine or cow) adj4 pericard*).tw. (1490)
9 PERIMOUNT aortic valve.tw. (8)

10 Heart Valve Prosthesis/ (34495)
11 ((aortic* or cardi* or heart*) adj4 (reconstruct* or repair* or replace* or prosthesi*)).tw. (44518)
12 Pericardium/tr (1533)
13 or/8-12 (70277)
14 Glutaral/ (7213)
15 glutaraldehyd*.tw. (15763)
16 or/14-15 (18129)
17 13 and 16 (1128)
18 7 and 17 (242)
19 Animals/ not Humans/ (4648315)
20 18 not 19 (199)
21 (201705* or 201706* or 2001707* or 201708* or 201709* or 20171*).ed. (430281)
22 20 and 21 (4)