Interventional procedure overview of aortic valve reconstruction using glutaraldehyde-treated autologous pericardium for aortic valve disease

Contents

Table 1 Abbreviations

Abbreviation	Definition
AI	Aortic insufficiency
AVA	Aortic valve area
AVNeo	Aortic valve neocuspidisation
EOA	Effective orifice area
EOAI	Effective orifice area index
iEOA	Indexed effective orifice area
LVOT	Left ventricle outflow tract
MPG	Mean pressure gradient
NYHA	New York Heart Association
PSM	Propensity score matching
SAVR	Surgical aortic valve replacement
SVD	Structural valve degeneration
TAVI	Transcatheter aortic valve implantation

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, syncope 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 or transcatheter aortic valve implantation (TAVI) with a biological prosthesis. Bioprosthetic and mechanical valves do not perform as well as native valves and have limited durability (mechanical valves last longer than bioprosthetic valves), 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 particularly in older patients and those with significant comorbidities. It is also 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.

The aortic valve reconstruction using glutaraldehyde-treated autologous pericardium is suitable for patients who cannot or do not wish 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 full or partial sternotomy and the patient is established on cardiopulmonary bypass. The heart is stopped with cardioplegic arrest. A portion of pericardium is harvested, and excessive adipose tissue removed. The excised pericardium is treated with glutaraldehyde and rinsed with saline to avoid drying. The aorta is opened and the valve is inspected. The diseased valve cusps are carefully removed. The intercommissural distances are measured using Ozaki sizers and the treated pericardium is trimmed to the desired size and stitched to the annulus to replace the removed valve leaflet(s). When aligned, the leaflets are stitched to the wall of the aorta to create a functional valve. The aorta is closed, the heart is de-aired and cardiopulmonary bypass is discontinued. The circulation is restored, and the chest closed. The function of the valve is assessed intraoperatively by transoesophageal echocardiography.

Outcome measures

The main outcomes included survival rates, reoperation rates, mortality and resolution of clinical symptoms or improvement in biochemical parameters, such as aortic valve pressure gradient and aortic valve function. Other outcomes included technical failure, cardiopulmonary bypass time, aortic cross-clamp time, length of intensive care unit stay, cusp calcification rates, in-hospital events and the risk of endocarditis. The measures used are detailed in the following paragraphs.

New York Heart Association (NYHA) heart failure classification

Class	Symptoms
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity, for example 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 because of symptoms, even during less-than-ordinary activity, for example 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 (ESC) and American Society of Echocardiography(ASE)

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[ESC])	20–40[ASE] (30–50[ESC])	>40[ASE] (>50[ESC])
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

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
Velocity time integral (VTI) diastolic flow reversal (upper descending aorta, cm)			15
Pressure half time (ms)	>500		<250

Evidence summary

Population and studies description

This interventional procedures overview is based on more than 30,000 patients from 1 meta-analysis (Mylonas 2023), 1 case series and meta-analysis (Benedetto 2021), 1 systematic review (Dilawar 2022), 1 case series (Halees 2005), 1 multicentre case series (Sá 2020), 1 non-randomised comparative study (Boehm 2022) and 2 case reports (Mikami 2022; Bernhardt 2021). Of these patients, about 5,000 patients had the procedure. There was some overlap in patients between studies and overlap in papers between systematic reviews and meta-analysis. Some of the studies summarised separately were also included in at least 1 of the reviews. The case series and meta-analysis by Benedetto et al. (2021) was included in the meta-analysis by Mylonas et al. (2023).

This is a rapid review of the literature, and a flow chart of the complete selection process is shown in figure 1. This overview presents 8 studies as the key evidence in table 2 and table 3, and lists 44 other relevant studies in table 5.

Of the 22 studies included in the meta-analysis by Mylonas et al. (2023), there were 15 cases series, 3 retrospective cohort studies, 1 prospective propensity score matching (PSM) cohort study, 1 prospective cohort study, 1 retrospective PSM cohort study and 1 case series and meta-analysis. The quality of included case series was assessed using the National Heart, Lung, and Blood Institute scale. The Newcastle-Ottawa Quality scale was used to evaluate the quality of case-control studies, with a score of at least 6 indicating high quality. In the item assessing whether the follow-up period was long enough for outcomes to occur, the cut-off value was set at 12 postoperative months per study, and a rate of 90% was used to define adequate follow up. All 7 of the studies for aortic valve neocuspidisation (AVNeo) included in Benedetto et al. (2021) were retrospective. Risk of bias in individual studies was assessed using the quality in prognostic studies instrument as per published protocol. Of the 12 studies included in Dilawar et al. (2022), all were retrospective single-centre series, 1 of which was a comparative study. The risk of bias of each study was measured using Methodological Index for Non-Randomized Studies (MINORS). The global ideal score was 16 and 24 for non-comparative and comparative studies, respectively.

Recruitment periods of the key evidence studies began in 1988 (Halees 2005). Follow-up periods, when reported, ranged from 12.5±0.9 months to 16 years.

The studies included in the meta-analysis and systematic review were done in various locations, including several countries in Europe, the US, China, and Japan, India and Vietnam. The other key evidence studies were done in the UK, Brazil, Russia, Germany, Saudi Arabia, Japan, Vietnam, and the US.

All studies included patients who had aortic valve reconstruction with glutaraldehyde-treated autologous pericardium. In the meta-analysis by Mylonas et al. (2023), the mean age was stratified to adult patients (65±12.3 years) and paediatric patients (12.3±3.8 years). Table 2 presents study details.

Figure 1 Flow chart of study selection

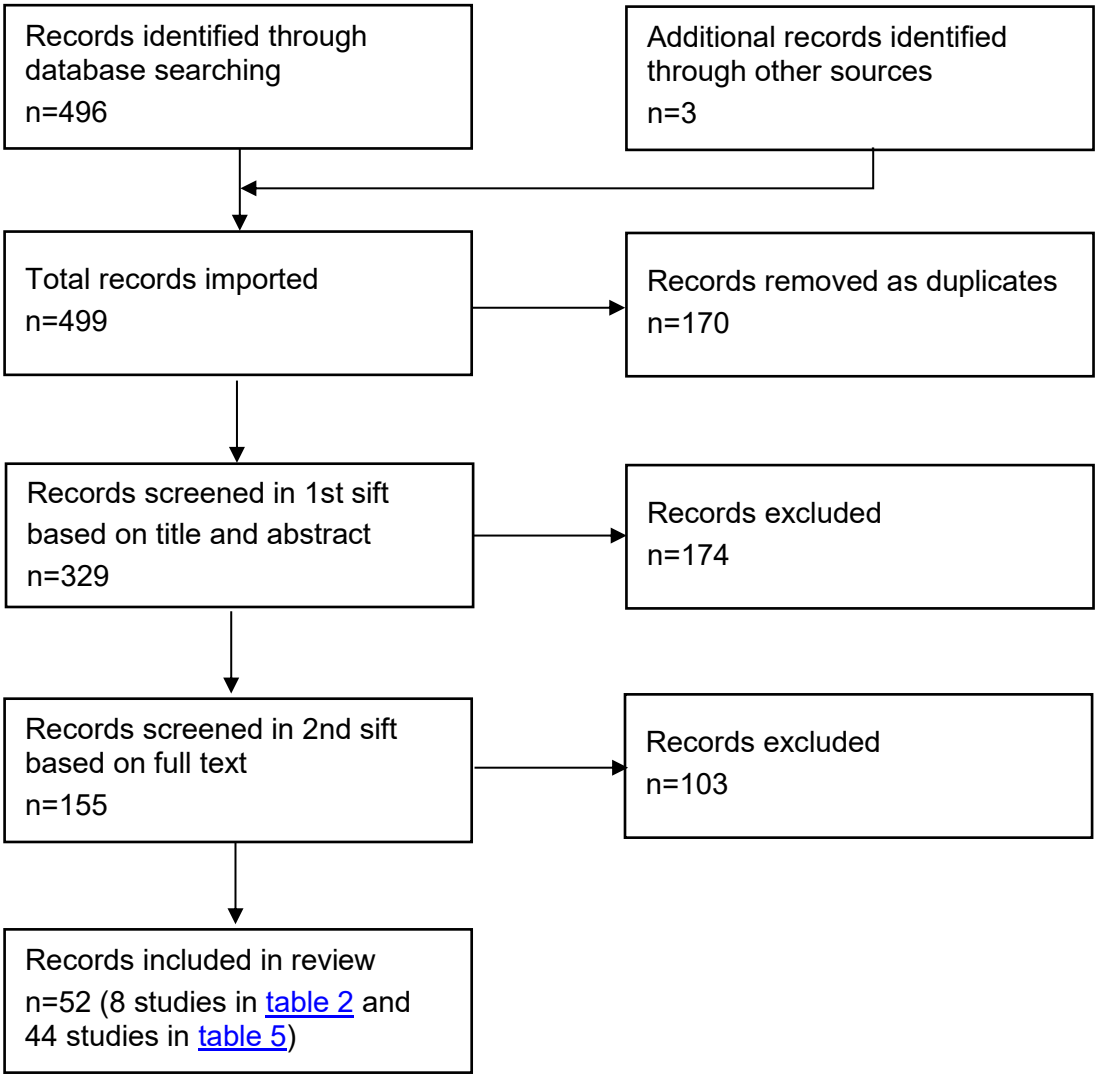

Table 2 Study details

Study no.	First author, date country	Patients (male: female)	Age	Study design	Inclusion criteria	Intervention	Follow up
1	Mylonas, 2023 Various	n=1,891 (49.6% male)	43.2±24.5 years (65±12.3 years for adult patients and 12.3±3.8 years for paediatric patients)	A meta-analysis of reconstructed patient-level data (22 studies)	Eligible literature comprised of original clinical studies which were published in English and reported on demographic, clinical characteristics, and outcomes of paediatric and adult patients undergoing AVNeo using the Ozaki technique. Publication year filters were employed since the original report on the Ozaki procedure was published in March 2011	Autologous pericardium was used in 90.6% of the included patients. 3.8% had AVNeo with xenologous pericardium. 5.6% used autologous pericardium in certain patients and xenologous products in others without separately reporting their outcomes	Mean follow up of 38.1± 23.8 months (maximum 9.8 years)
2	Benedetto, 2021 UK, Various	n=55 (61.8% male)	Mean age 58±15 years	Case series	AVNeo using autologous pericardium in adult patients (>18 years old) was done in University Hospitals Bristol NHS Foundation Trust and University Hospital Coventry & Warwickshire from 2018 to 2020	AVNeo using autologous pericardium	12.5±0.9 months

Study no.	First author, date country	Patients (male: female)	Age	Study design	Inclusion criteria	Intervention	Follow up
		39 studies. AVNeo: n=1,205 Trifecta: n=8,705 Magna Ease: n=3,137 Freedom Solo: n=1,869 Freestyle: n=4,307 Mitroflow: n=4,760 Autograft aortic valve: n=3,839	Mean age ranged from 52 to 78 years for AVNeo studies	Meta-analytic comparison (39 studies)	Procedures done with autologous pericardium in adult patients (>18 years) with follow-up data available	AVNeo with autologous pericardium – 7 studies Trifecta – 10 studies Magna Ease – 3 studies Freedom Solo – 4 studies Freestyle – 4 studies Mitroflow – 4 studies Autograft aortic valve – 7 papers Outcomes of interest were the incidence of structural valve degeneration (SVD), endocarditis and reintervention	Not reported

Study no.	First author, date country	Patients (male: female)	Age	Study design	Inclusion criteria	Intervention	Follow up
3	Dilawar, 2022 Various	n=1,427 (52.1% male)	Mean age 64.95 years	A systematic review (12 studies)	Studies investigating the outcome of aortic valve replacement with autologous pericardium	Aortic valve replacement with autologous pericardium	Not reported
4	Sá, 2020 Brazil, Russia and Germany	n=106 (35.9% male)	Mean age was 65.4 (range, 38–80 years)	A multicentre study	Patients with small aortic annulus (≤21 mm) and aortic valve diseases from Jan 2017 to Mar 2019 at 3 centres	AVNeo procedure	Not reported
5	Boehm, 2022 Germany	n=563 (71.6% male)	Mean age 51.3±15.6 years for AVNeo 67.0±8.8 years for surgical aortic valve replacement (SAVR)	Non-randomised comparative study	Patients who underwent either AVNeo or SAVR between March 2017 and Aprial 2020. AVNeo patients were only included if they had intraoperative measurement of the annulus	AVNeo for trileaflet aortic valve reconstruction using autologous pericardium (Ozaki procedure)	Not reported

Study no.	First author, date country	Patients (male: female)	Age	Study design	Inclusion criteria	Intervention	Follow up
6	Halees, 2005 Saudi Arabia	n=92 (65% male)	Mean age 30 years	Case series	Aortic valve reconstruction with pericardium between 1988 and 1995	Aortic valve reconstruction with bovine pericardium (n=27). Aortic valve reconstruction with glutaraldehyde-treated autologous pericardium (n=65)	16 years
Safety studies – the following studies were included to show unique safety events							
7	Mikami, 2022 Japan	n=1 (male)	56 years	Case report	Not reported	AVNeo using autologous pericardium (Ozaki procedure) for aortic stenosis	Not reported
8	Bernhardt, 2021 US	n=1 (male)	56 years	Case report	Not reported	Aortic valve reconstruction using the Ozaki procedure	Not reported

Table 3 Study outcomes (option 1)

First author, date	Efficacy outcomes	Safety outcomes

Mylonas, 2023	**Survival** Based on the reconstructed individual patient data, 1-year, 3-year, and 5-year survival rates were 93.1%, 90.5%, and 87.5%, respectively. **Reoperation** Overall, 1-year, 3-year, and 5-year freedom from reoperation rates were 98.0%, 97.0%, and 96.5%, respectively. The most common indication for reoperation was infective endocarditis (n=29; 51.5%, 95% CI 18.3 to 84.0), followed by structural valve deterioration (n=10; 34.8%, 95% CI 17.9 to 54.3), while only 2 patients needed redo surgery because of cusp tears. **Technical failure** Ozaki procedure was intraoperatively abandoned in 0.6% (95% CI 0.3 to 1.1) of the patients, who subsequently had conventional aortic valve replacement. **Cardiopulmonary bypass time** Mean cardiopulmonary bypass time was 135.2 (±35.1) minutes. **Aortic cross-clamp time** Mean aortic cross-clamp time was 106.8 (±24.8) minutes. **Aortic valve pressure gradient**	**Mortality** In-hospital mortality was 0.7% (95% CI 0.1 to 1.7, I^2=20%, p=0.21). There were no in-hospital paediatric fatalities, while 1.3% (95% CI 0.3 to 2.6, I^2=31%, p=0.11) of adult patients died in hospital. 1.1% (95% CI 0.2 to 2.4, I^2=32%, p=0.13) of the patients in the autologous pericardium group died in hospital, while there were no in-hospital mortalities in the xenologous pericardium cohort. Late mortality was 1.9% (95% CI 0.2 to 4.7, I^2=78%, p<0.001) during a mean follow up of 38.1±23.8 months (maximum 9.8 years). In the adult cohort, late mortality rates were 2.7% (95% CI 0.4 to 6.3, I^2= 84%, p<0.001), while in the paediatric group late mortality was 0.6% (95% CI 0.0 to 3.9, I^2=0%, p=0.98). Patients that had Ozaki reconstruction using autologous pericardium had a 2.0% (95% CI 0.1 to 5.5, I^2=82%, p<0.001) late mortality rate, while no fatality was noted in the xenologous pericardium group. **In-hospital events** 2 patients needed redo surgery because of cusp tears. **Cusp calcification** Premature calcification of the neo-leaflets was identified in most patients. **Endocarditis** Infective endocarditis (n=29; 51.5%, 95% CI 18.3 to 84.0) leading to reoperation. The risk of endocarditis per patient per year was 0.5%.

First author, date	Efficacy outcomes	Safety outcomes
	Preoperative peak and mean pressure gradient (MPG) were estimated at 74.5±21.6 mmHg and 58.7±29.5 mmHg, respectively. The mean postoperative peak and MPG were 17.4±9.2 mmHg and 7.7±3.7 mmHg, respectively. Late peak and MPG were 15.7±7.4 mmHg and 11.4±6.4 mmHg, respectively **Aortic valve function** At latest follow up, 36.8% (95% CI 15.4 to 61.2) of the patients had trace aortic regurgitation, 4.7% (95% CI 1.1 to 10.1) had minor, and only 0.2% (95% CI 0 to 2.3) had moderate aortic insufficiency (AI). No cases of severe AI have been reported following Ozaki procedures. **Length of intensive care unit stay** Mean length of intensive care unit stay was 3.3±5.1 days.	

Benedetto, 2021	**Case series:** **Survival** 55 patients treated by AVNeo with autologous pericardium survival was 96% (53/55) at a mean follow up of 12.5±0.9 months. **Reoperation** 2% (1/55) had reintervention. Freedom from death, endocarditis, reintervention and SVD was 92.5%±3.6%. **Cardiopulmonary bypass time** Mean cardiopulmonary bypass time was 136.0 (114.5–166.0) minutes. **Aortic cross-clamp time** Mean aortic cross-clamp time was 108.0 (95.0–131.5) minutes. **Aortic valve pressure gradient** Very low postoperative peak and mean transvalvular gradients (16±3.7 and 9±2.2 mmHg), respectively. **Aortic valve function** There was a significant improvement in NYHA class compared to baseline with all but 2 patients in NYHA class I–II ($p<0.001$).	**Mortality** In-hospital deaths were reported in 2% (1/55) of patients. Late deaths were reported in 2% (1/55) of patients. **In-hospital events** Postoperative course was uneventful for all but an 80-year-old patient who developed pneumonia, respiratory failure and later died of sepsis. **Endocarditis** Three patients presented with endocarditis at follow up (2 new occurrences of endocarditis after 5 and 12 months from index operation with 1 patient requiring aortic reintervention and 1 recurrence of endocarditis after 2 months from index operation). Freedom from death, endocarditis, reintervention and SVD was 92.5%±3.6%.

First author, date	Efficacy outcomes	Safety outcomes
	Length of intensive care unit stay Mean length of intensive care unit stay was 5 (SD=5.03) days.	
	Meta-analytic comparisons: **Reoperation** AVNeo was associated with an incidence rate of 1.07%/patient-year for reoperation. When the series by Ozaki was removed, pooled estimates were 0.14%/patient-year for reoperation.	**In-hospital events** AVNeo showed a similar incidence of valve-related events compared to most valve substitutes included in the analysis like Trifecta, Magna Ease, Freedom Solo, Freestyle, Mitroflow and autograft AV. **Endocarditis** AVNeo was associated with an incidence rate of 0.45%/patient-year for endocarditis. When the series by Ozaki was removed, pooled estimates were 0.58%/patient-year for endocarditis.

First author, date	Efficacy outcomes	Safety outcomes
Dilawar, 2022	**Reoperation** Reoperation was reported in 16 (1.12%) patients. **Aortic valve pressure gradient** All studies in this review reported improvement of haemodynamic performance 1 week after surgery or at discharge. The average preoperative peak pressure gradient ranged from 66.0±28.2 to 92.0±31.2 mmHg, while the postoperative peak pressure gradient ranged from 10.6±3.3 to 23.4±10.7 mmHg.	**Mortality** Of 1,427 patients, 25 (1.75%) died. 16% of all mortality had a cardiac cause including leaflet dehiscence which eventually led to multiorgan dysfunction syndrome, endocarditis/paravalvular abscess, cardiac tamponade, and fatal thoracic haemorrhage. Most occurred immediately after surgery or within 1 year after discharge. Non-cardiac causes of mortality including pneumonia, cancer, etc. mostly occurred later, years after patients had been discharged. **In-hospital events** There were 3 (0.21%) and 13 (0.91%) thromboembolic and endocarditis events that occurred respectively. **Cusp calcification** One study reported valve extension with glutaraldehyde-preserved autologous pericardium in mitral valve repair. In their series, they found no calcification of autologous pericardium in 64 cases with 6 months to 9 years of follow up. **Endocarditis** Reoperation were reported in 16 (1.12%) patients, mainly because of endocarditis (69%).

Sá, 2020	**Reoperation** Four patients needed reoperation for bleeding (2 for suture hole bleeding of the aortic wall; 1 for bleeding of the venous cannulation site in the right atrium; 1 for bleeding because of injury to 1 of the internal mammary veins during the placement of sternal wires). **Technical failure** One patient required pacemaker implantation. After the AVNeo procedure, 24 (22.6%) patients had a mild aortic regurgitation because of central leak. **Cardiopulmonary bypass time** Mean cardiopulmonary bypass time was 109.5±35.0 min. **Aortic cross-clamp time** Mean aortic cross-clamp time was 84.4±19.7 min. **Aortic valve pressure gradient** Average peak and MPGs were 11.8±5.9 mmHg and 7.3±3.5 mmHg (mean±SD), respectively, after surgery. **Aortic valve function** Effective orifice area (EOA) and indexed EOA (iEOA) averaged 2.5±0.4 cm^2 and 1.3±0.3 cm^2/m^2 after surgery, respectively. EOA and iEOA significantly increased by 1.8±0.1 cm^2 ($p<0.001$) and 0.9±0.1 cm^2/m^2 ($p<0.001$), respectively, in comparison to preoperative measures.	**Mortality** There were 2 in-hospital deaths because of non-cardiac causes. **In-hospital events** No thromboembolic events were recorded **Endocarditis** No patient needed reoperation because of early infective endocarditis.

First author, date	Efficacy outcomes	Safety outcomes
	Length of intensive care unit stay Median intensive care unit was 1.5±1.2 days.	

First author, date	Efficacy outcomes	Safety outcomes
Boehm, 2022	**Cardiopulmonary bypass time** Mean cardiopulmonary bypass time was 163.1 (±33.4) minutes in the AVNeo group and 112.62 (±40.2) minutes in the SAVR group. **Aortic cross-clamp time** Mean aortic cross-clamp time was 136.1 (±22) minutes in the AVNeo group and 85.4 (±31.5) minutes in the SAVR group. **Aortic valve pressure gradient** MPGs were lower in the AVNeo group than in the SAVR group (AVNeo: MPG=8.0 mmHg ± 3.6 versus SAVR: MPG=8.3 mmHg ±3.6). **Aortic valve function** At discharge, the AVNeo group revealed statistically significantly larger EOAs (AVNeo group: EOA=2.4 cm^2±0.8 versus SAVR group: EOA = 2.1 cm^2±0.5, respectively; p<0.001). Effective orifice area index (EOAI) was greater in the AVNeo group, with an average EOAI=1.23 cm^2/m^2±0.4 in the AVNeo cohort versus 1.02 cm^2/ m^2±0.3 in the SAVR group (p<0.001).	**In-hospital events** Four patients in the AVNeo group (3.8%) had a severe mismatch with an EOAI<0.65 cm^2/m^2 versus 14 (3.6%) patients in the SAVR cohort (p=0.557).

Halees, 2005 Saudi Arabia	**Survival** In 92 patients treated by aortic valve reconstruction 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. **Reoperation** At 16 years, 28 patients remain with no reoperation in the autologous pericardium group. Causes of reoperation in the autologous pericardium group were endocarditis (7/65), mitral/tricuspid valve disease (2/65), structural valve degeneration (17/65) and aortic valve regurgitation (1/65). **Cardiopulmonary bypass time** Mean cardiopulmonary bypass time was 150 (±33) minutes in the bovine pericardium group and 129 (±25) minutes in the autologous pericardium group. **Aortic cross-clamp time** Mean aortic cross-clamp time was 100 (±20) minutes in the bovine pericardium group and 95 (±20) minutes in the autologous pericardium group. **Aortic valve function** 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%	**Mortality** In-hospital deaths from cardiac causes were reported in 3% (2/65) of patients treated by aortic valve reconstruction using autologous pericardium. Late deaths from cardiac causes were reported in 3% (2/65) of patients in the autologous pericardium group. Death at reoperation was reported in 2% (1/65) of patients in the autologous pericardium group. **Cusp calcification** Cusp calcification was reported in 1/28 patients in the autologous pericardium group. **Endocarditis** Endocarditis leading to reoperation was reported in 11% (7/65) of patients who had aortic valve reconstruction using autologous pericardium.

First author, date	Efficacy outcomes	Safety outcomes
	[6/28]) and severely impaired (1/28) in the autologous pericardium group, at 16-years follow up.	
Safety studies – the following studies were included to show unique safety events		
Mikami, 2022	Not reported	A 56-year-old man with a history of left nephrectomy for Wilms' tumour on chronic haemodialysis had AVNeo using autologous pericardium (Ozaki procedure) for aortic stenosis because of a bicuspid aortic valve 6 years ago. The aortic stenosis gradually progressed and a decrease in the left ventricular ejection fraction was observed. He underwent a reoperative aortic valve replacement using a mechanical valve. Intraoperative findings showed severe calcification at the site where the autologous pericardium was sutured to the annulus. However, the degeneration of the valve leaflets themselves was mild.
Bernhardt, 2021	Not reported	A 56-year-old male presented with aortic valve endocarditis and severe AI. He underwent successful aortic valve reconstruction by the Ozaki procedure. It was complicated by postpericardiotomy syndrome and cardiac tamponade after the procedure.

Procedure technique

Of the 8 studies, 4 detailed the procedure technique of aortic valve reconstruction with glutaraldehyde-treated autologous pericardium. Only 1 study (Halees, 2005) treated autologous pericardium with a 0.5% buffered glutaraldehyde solution for 10 minutes and rinsed it for 10 minutes before use. This was used before Ozaki technique developed. The other 3 studies (Benedetto, 2021; Boehm, 2022; Sá, 2020) treated autologous pericardium with a 0.6% glutaraldehyde solution and rinsed it 3 times for 6 minutes with sterile saline before use. In the meta-analysis (Mylonas, 2023), autologous pericardium was used in 91% of the included patients, while only 4% had AVNeo with xenologous pericardium, and 6% used autologous pericardium in certain patients and xenologous products in others without separately reporting their outcomes. In the meta-analytic comparison (Benedetto, 2021), there were 10 studies that used other biological valve substitutes. All other studies used aortic valve reconstruction with glutaraldehyde-treated autologous pericardium.

Efficacy

Survival

Survival of aortic valve reconstruction with glutaraldehyde-treated autologous pericardium was reported in 3 studies and ranged from 88% to 96%. In the meta-analysis of 22 studies (n=1,891), based on the reconstructed individual patient data, the rate of survival at 1-year, 3-year, and 5-year were 93%, 91%, and 88%, respectively (Mylonas 2023).

In a case series of 55 patients, the survival rate was 96% (53/55) at a mean follow up of 12.5±0.9 months (Benedetto 2021).

In a case series of 92 patients treated by aortic valve reconstruction, 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 (Halees 2005).

Reoperation

Reoperation of aortic valve reconstruction with glutaraldehyde-treated autologous pericardium was reported in 6 studies and ranged from 1% to 57%. In the meta-analysis of 22 studies, the rate of reoperation at 1, 3 and 5 years, were 2%, 3% and 4%, respectively. The most common indication for reoperation was infective endocarditis (n=29; 51.5%, 95% CI 18.3 to 84.0), followed by structural valve deterioration (n=10; 34.8%, 95% CI 17.9 to 54.3), while only 2 patients needed redo surgery because of cusp tears (Mylonas 2023).

In a case series of 55 patients, reoperation rate was 2% (1/55). In the meta-analytic comparison of 39 studies, reoperation rate was 1%/patient-year for aortic valve neocuspidisation. When the series by Ozaki was removed, pooled estimates for reoperation were less than 1%/patient-year (Benedetto 2021).

In a systematic review of 12 studies, reoperation rate was 1% (16/1,427) (Dilawar 2022).

In a multicentre study of 106 patients, reoperation rate was less than 4% (4/106). All 4 reoperations were for bleeding: 2 for suture hole bleeding of the aortic wall; 1 for bleeding of the venous cannulation site in the right atrium; 1 for bleeding because of injury to 1 of the internal mammary veins during the placement of sternal wires (Sá 2020).

In a case series of 92 patients, reoperation rate was 57% (37/65) at 16-year follow up. Reasons for reoperation in the autologous pericardium group were endocarditis (11%), mitral/tricuspid valve disease (less than 1%), structural valve degeneration (26%) and aortic valve regurgitation (less than 1%) (Halees 2005).

Technical failure

Technical failure of aortic valve reconstruction with glutaraldehyde-treated autologous pericardium was reported in 2 studies and ranged from 1% to 23%. In the meta-analysis of 22 studies, the Ozaki procedure was intraoperatively abandoned in less than 1% (95% CI 0.3 to 1.1) of patients, who subsequently had conventional aortic valve replacement (Mylonas 2023).

In a multicentre study of 106 patients, less than 1% (1/106) of patients needed pacemaker implantation (Sá 2020).

Cardiopulmonary bypass time

Cardiopulmonary bypass time during aortic valve reconstruction with glutaraldehyde-treated autologous pericardium was reported in 5 studies and ranged from 74.5 minutes to 170.3 minutes. In the meta-analysis of 22 studies. mean cardiopulmonary bypass time was 135.2 (±35.1) minutes (Mylonas 2023).

In the case series of 55 patients, mean cardiopulmonary bypass time was 136.0 (114.5–166.0) minutes (Benedetto 2021).

In the multicentre study of 106 patients, mean cardiopulmonary bypass time was 109.5±35.0 minutes (Sá 2020).

In the non-randomised comparative study of 563 patients, mean cardiopulmonary bypass time was 163.1 (±33.4) minutes in the AVNeo group and 112.62 (±40.2) minutes in the SAVR group (Boehm 2022).

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 (Halees 2005).

Aortic cross-clamp time

Aortic cross-clamp time during aortic valve reconstruction with glutaraldehyde-treated autologous pericardium was reported in 5 studies and ranged from

64.7 minutes to 158.1 minutes. In the meta-analysis of 22 studies, mean aortic cross-clamp time was 106.8 (±24.8) minutes (Mylonas 2023).

In the case series of 55 patients, mean aortic cross-clamp time was 108.0 (95.0–131.5) minutes (Benedetto 2021).

In the multicentre study of 106 patients, mean aortic cross-clamp time was 84.4±19.7 minutes (Sá 2020).

In the non-randomised comparative study of 563 patients, mean aortic cross-clamp time was 136.1 (±22) minutes in the AVNeo group and 85.4 (±31.5) minutes in the SAVR group (Boehm 2022).

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 (Halees 2005).

Aortic valve pressure gradient

Aortic valve pressure gradient was reported in 5 studies. In the meta-analysis of 22 studies, preoperative peak and MPG were estimated at 74.5±21.6 mmHg and 58.7±29.5 mm Hg, respectively. Mean postoperative peak and MPG were 17.4±9.2 mmHg and 7.7±3.7 mmHg respectively. Late peak and MPG were 15.7±7.4 mmHg and 11.4±6.4 mmHg, respectively (Mylonas 2023).

In the case series of 55 patients, peak and mean transvalvular gradients were 16±3.7 and 9±2.2 mmHg, respectively (Benedetto 2021).

In a systematic review of 12 studies, improvement of haemodynamic performance 1 week after surgery or at discharge was reported. The average preoperative peak pressure gradient ranged from 66.0±28.2 to 92.0±31.2 mmHg, while the postoperative peak pressure gradient ranged from 10.6±3.3 to 23.4±10.7 mmHg (Dilawa, 2022).

In the multicentre study of 106 patients, average postoperative peak and MPG were 11.8±5.9 mmHg and 7.3±3.5 mmHg (mean±SD), respectively (Sá 2020).

In the non-randomised comparative study of 563 patients, MPG in the AVNeo group were 8.0 mmHg±3.6, while MPG in the SAVR group were 8.3 mmHg±3.6 (Boehm 2022).

Aortic valve function

Aortic valve function after aortic valve reconstruction with glutaraldehyde-treated autologous pericardium was reported in 5 studies. In the meta-analysis of 22 studies, 37% (95% CI 15.4 to 61.2) of the patients had trace AR, 5% (95% CI 1.1–10.1) had minor AI, and less than 1% (95% CI 0 to 2.3) had moderate AI at latest follow up. No cases of severe AI have been reported following Ozaki procedures (Mylonas 2023).

In the case series of 55 patients, there was a significant improvement in NYHA class compared to baseline with all but 2 patients in class NYHA I–II ($p<0.001$) (Benedetto 2021).

In the multicentre study of 106 patients, effective orifice area (EOA) and indexed EOA (iEOA) averaged 2.5±0.4 cm^2 and 1.3±0.3 cm^2/m^2 after surgery, respectively. EOA and iEOA significantly increased by 1.8±0.1 cm^2 ($p<0.001$) and 0.9±0.1 cm^2/m^2 ($p<0.001$), respectively, in comparison to preoperative measures (Sá 2020).

In the non-randomised comparative study of 563 patients, the AVNeo group revealed significantly larger EOAs (AVNeo group: EOA=2.4 cm^2±0.8 versus SAVR group: EOA=2.1 cm^2±0.5, respectively; $p<0.001$) at discharge. EOAI was greater in the AVNeo group, with an average EOAI =1.23 cm^2/m^2±0.4 in the AVNeo cohort versus 1.02 cm^2/ m^2±0.3 in the SAVR group ($p<0.001$) (Boehm 2022).

In the case series of 92 patients, 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 (Halees 2005).

Length of intensive care unit stay

Length of intensive care unit stay after aortic valve reconstruction with glutaraldehyde-treated autologous pericardium was reported in 3 studies. In the meta-analysis of 22 studies, mean length of intensive care unit stay was 3.3±5.1 days (Mylonas 2023).

In the case series of 55 patients, mean length of intensive care unit stay was 5 (SD=5.03) days (Benedetto 2021).

In the multicentre study of 106 patients, median intensive care unit was 1.5±1.2 days (Sá 2020).

Safety

Mortality

Mortality was reported in 5 studies. In the meta-analysis of 22 studies, in-hospital mortality was less than 1% (95% CI 0.1 to 1.7, I^2=20%, p=0.21). There were no in-hospital paediatric deaths, while the rate of in-hospital deaths for adults was 1% (95% CI 0.3 to 2.6, I^2=31%, p=0.11). In the autologous pericardium group, in-hospital mortality was 1% (95% CI 0.2 to 2.4, I^2=32%, p=0.13) while there were no in-hospital deaths in the xenologous pericardium cohort. Late mortality was 2% (95% CI 0.2 to 4.7, I^2=78%, p< 0.001) during a mean follow up of 38.1±23.8 months (maximum 9.8 years). In the adult cohort, late mortality rates were 3% (95% CI 0.4 to 6.3, I^2=84%, p<0.001), while in the paediatric group late mortality was 0.6% (95% CI 0.0 to 3.9, I^2 =0%, p=0.98). Patients that had Ozaki

reconstruction using autologous pericardium had a 2% (95% CI 0.1 to 5.5, I^2=82%, p<0.001) late mortality rate, while no fatality was noted in the xenologous pericardium group (Mylonas 2023).

In the case series of 55 patients, there was 1 in-hospital death and 1 late death (Benedetto 2021).

In a systematic review of 12 studies, 2% (25/1427) of patients died.16% of all mortality had a cardiac cause, including leaflet dehiscence which eventually led to multiorgan dysfunction syndrome, endocarditis/paravalvular abscess, cardiac tamponade, and fatal thoracic haemorrhage. Most occurred immediately after surgery or within 1 year after discharge. Non-cardiac causes of mortality including pneumonia, cancer, etc. mostly occurred later, years after patients had been discharged (Dilawar 2022).

In the multicentre study of 106 patients, less than 2% (2/106) of patients had in-hospital deaths, which was both because of non-cardiac causes (Sá 2020).

In the case series of 92 patients, in-hospital deaths from cardiac causes were reported in 3% (2/65) of patients treated by aortic valve reconstruction using autologous pericardium. Late deaths from cardiac causes were reported in 3% (2/65) of patients in the autologous pericardium group. Death at reoperation was reported in 2% (1/65) of patients in the autologous pericardium group (Halees 2005).

In-hospital events

In-hospital events after aortic valve reconstruction with glutaraldehyde-treated autologous pericardium was reported in 5 studies. In the meta-analysis of 22 studies, 2 patients had reoperation because of cusp tears (Mylonas 2023).

In the case series of 55 patients, the postoperative course was uneventful for all but 1 patient (80-year-old) who developed pneumonia, respiratory failure and later died of sepsis. In the meta-analytic comparison of 39 studies, AVNeo showed a similar incidence of valve-related events compared to other valve substitutes included in the analysis and autograft AV (Benedetto 2021).

In a systematic review of 12 studies, there were 3 (less than 1%) and 13 (less than 1%) thromboembolic and endocarditis events that occurred respectively (Dilawar 2022).

In the multicentre study of 106 patients, no thromboembolic events were recorded (Sá 2020).

In the non-randomised comparative study of 563 patients, 4% (4/105) of patients of the AVNeo group and 4% (14/458) of patients in the SAVR cohort had a severe mismatch with an EOAI<0.65 cm^2/m^2 (p=0.557) (Boehm 2022).

Cusp calcification

Cusp calcification was reported in 3 studies. In the meta-analysis of 22 studies, premature calcification of the neo-leaflets was identified in most patients(Mylonas 2023).

In a systematic review of 12 studies, 1 study reported valve extension with glutaraldehyde-preserved autologous pericardium in mitral valve repair. In their series, they found no calcification of autologous pericardium in 64 cases with 6 months to 9 years of follow up (Dilawar 2022).

In the case series of 92 patients, cusp calcification was reported in less than 4% (1/28) patients in the autologous pericardium group (Halees 2005).

Endocarditis

Cusp calcification was reported in 3 studies. In the meta-analysis of 22 studies, 52% of patients who needed reoperation had infective endocarditis (95% CI 18.3

to 84.0). The risk of endocarditis per patient per year was less than 1% (Mylonas 2023).

In the case series of 55 patients, 3 patients presented with endocarditis at follow up (2 new occurrences of endocarditis after 5 and 12 months from index operation with 1 patient needing aortic reintervention and 1 recurrence of endocarditis after 2 months from index operation). In the meta-analytic comparison of 39 studies, AVNeo was associated with an incidence rate of less than 1%/patient-year for endocarditis. When the series by Ozaki was removed, pooled estimates were less than 1%/patient-year for endocarditis (Benedetto 2021).

In a systematic review of 12 studies, endocarditis was the reason for 69% of reoperations (Dilawar 2022).

In the multicentre study of 106 patients, no patient needed reoperation because of early infective endocarditis (Sá 2020).

In the case series of 92 patients, endocarditis leading to reoperation was reported in 11% (7/65) of patients who had aortic valve reconstruction using autologous pericardium (Halees 2005).

Other

In a case report, a 56-year-old man on chronic haemodialysis with a history of left nephrectomy for Wilms' tumour had AVNeo using autologous pericardium (Ozaki procedure) for aortic stenosis because of a bicuspid aortic valve 6 years ago. The aortic stenosis gradually progressed and a decrease in the left ventricular ejection fraction was observed. He had a reoperative aortic valve replacement using a mechanical valve. Intraoperative findings showed severe calcification at the site where the autologous pericardium was sutured to the annulus. However, the degeneration of the valve leaflets themselves was mild (Mikami 2022).

A 56-year-old male presented with aortic valve endocarditis and severe AI. He underwent successful aortic valve reconstruction by the Ozaki procedure. It was complicated by post-pericardiotomy syndrome and cardiac tamponade after the procedure (Bernhardt 2021).

Anecdotal and theoretical adverse events

Expert advice was sought from consultants who have been nominated or ratified by their professional society or royal college. They were asked if they knew of any other adverse events for this procedure that they had heard about (anecdotal), which were not reported in the literature. They were also asked if they thought there were other adverse events that might possibly occur, even if they had never happened (theoretical).

They listed the following anecdotal adverse events:

- Early fibrosis of the leaflets (1 patient developed a thrombus on 1 of the leaflets within a year of the procedure), early failure and regurgitation of the newly constructed aortic valve.

They listed the following theoretical adverse events:

- Increased risk of postoperative aortic regurgitation.
- Clot formation and embolisation.
- The valve reconstruction is not successful, and patient might need a prosthetic valve (this is normally done at the same operation so does prolong the operation slightly but with minimal risk).
- Infective endocarditis (this is a potential complication for any cardiac procedure and in fact using prosthetic valves increases the risk of endocarditis while having autologous pericardium in the aortic position would decrease it).

- Failure of the valve at follow up (this has been noted in the very young population 5–10-years-old as in same cases the leaflets have calcified).

Four professional expert questionnaires for this procedure were submitted. Find full details of what the professional experts said about the procedure in the specialist advice questionnaires for this procedure.

Validity and generalisability

- No randomised controlled trials on aortic valve reconstruction with glutaraldehyde-treated autologous pericardium were identified. Eight studies were included in the key evidence summary, including 1 meta-analysis, 1 case series and meta-analytic comparison study, 1 systematic review, 2 case series, 1 non-randomised comparative study and 2 case reports. Most of the evidence in the meta-analysis and systematic review is from case series or retrospective cohort studies.

- Research was done in various countries worldwide, including the UK.

- The procedures were done by specialists with training in tertiary referral centres.

- There is a lack of long-term outcomes of AVNeo. The longest mean or median follow up was 16 years, but this was a case series published in 2005 (Halees 2005).

- In the meta-analysis, paediatric series were included and there was a direct comparison between autologous to xenologous pericardium for AVNeo. There was limited evidence to compare Ozaki technique to aortic valve reconstruction or to the Ross procedure. The choice of pericardium does not seem to influence patient outcomes (Mylonas 2023).

- AVNeo's midterm risk of valve-related events is comparable to most biological valve substitutes (Benedetto 2021).

- In 1 non-randomised study comparing AVNeo with SAVR, AVNeo showed superior results for EOA and EOAI at discharge compared to replacement with a surgical aortic valve bioprosthesis. Long-term follow up is needed (Boehm 2022).

- None of the papers included in tables 2 and 3 reported that the study was funded by a company.

Related NICE guidance

Interventional procedures

- NICE's interventional procedures guidance 700 (2021) on Percutaneous insertion of a closure device to repair a paravalvular leak around a replaced mitral or aortic valve (Recommendation: special arrangements)
- NICE's interventional procedures guidance 653 (2019) on Valve-in-valve TAVI for aortic bioprosthetic valve dysfunction (Recommendation: standard arrangements)
- NICE's interventional procedures guidance 604 (2018) on Aortic valve reconstruction with processed bovine pericardium (Recommendation: research only)
- NICE's interventional procedures guidance 624 (2018) on Sutureless aortic valve replacement for aortic stenosis (Recommendation: standard arrangements)
- NICE's interventional procedures guidance 613 (2018) on Percutaneous balloon valvuloplasty for fetal critical aortic stenosis (Recommendation: research only)

- NICE's interventional procedures guidance 586 (2017) on Transcatheter aortic valve implantation for aortic stenosis (Recommendation: standard arrangements)
- NICE's interventional procedures guidance 78 (2004) on Balloon valvuloplasty for aortic valve stenosis in adults and children (Recommendation: standard arrangements)

NICE guidelines

- NICE clinical guideline 208 (2021) on Heart valve disease presenting in adults: investigation and management

Professional societies

- Society for Cardiothoracic Surgery in Great Britain and Ireland
- British Cardiovascular Society
- British Cardiovascular Intervention Society
- British Congenital Cardiac Association (BCCA)
- British Heart Value Society

Evidence from patients and patient organisations

NICE received 13 questionnaires from patients who had the procedure (or their carers).

Patients' views on the procedure were consistent with the published evidence and the opinions of the professional experts. See the patient commentary summary for more information.

Company engagement

NICE asked companies who manufacture a device potentially relevant to this procedure for information on it. NICE received 1 completed submission. This was considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

References

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4. Dilawar I, Putra M, Makdinata W et al. (2022) Autologous pericardium for adult and elderly patients undergoing aortic valve replacement: A systematic review. Cirugía Cardiovascular 29: 25-30
5. 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.
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7. Mylonas K, Tasoudis P, Pavlopoulos D et al. (2023) Aortic valve neoscuspidization using the Ozaki technique: A meta-analysis of reconstructed patient-level data. American heart journal 255:1-11
8. Sá M, Chernov I, Marchenko A et al. (2020) Aortic Valve Neocuspidization (Ozaki Procedure) in Patients with Small Aortic Annulus (≤21 mm): A Multicenter Study. Structural Heart. 4(5): 413-419.

Methods

NICE identified studies and reviews relevant to aortic valve reconstruction with glutaraldehyde-treated autologous pericardium from the medical literature. The following databases were searched between the date they started to 19/10/2022: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the internet were also searched (see the literature search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following inclusion criteria were applied to the abstracts identified by the literature search.

- Publication type: clinical studies were included with emphasis on identifying good quality studies. Abstracts were excluded if they did not report clinical outcomes. Reviews, editorials, and laboratory or animal studies, were also excluded and so were conference abstracts, because of the difficulty of appraising study methodology, unless they reported specific adverse events that not available in the published literature.
- Patients with aortic valve diseases.
- Intervention or test: aortic valve reconstruction with glutaraldehyde-treated autologous pericardium.
- Outcome: articles were retrieved if the abstract contained information relevant to the safety, efficacy, or both.

If selection criteria could not be determined from the abstracts the full paper was retrieved.

Potentially relevant studies not included in the main evidence summary are listed in the section on other relevant studies.

Find out more about how NICE selects the evidence for the committee.

Table 4 literature search strategy

Databases	Date searched	Version/files
MEDLINE (Ovid)	19/10/2022	1946 to October 18, 2022
MEDLINE In-Process (Ovid)	19/10/2022	1946 to October 18, 2022
MEDLINE Epubs ahead of print (Ovid)	19/10/2022	October 18, 2022
EMBASE (Ovid)	19/10/2022	1974 to 2022 October 17
EMBASE Conference (Ovid)	19/10/2022	1974 to 2022 October 17
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	19/10/2022	Issue 10 of 12, October 2022
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	19/10/2022	Issue 10 of 12, October 2022
International HTA database (INAHTA)	19/10/2022	-

Trial sources searched

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

Websites searched

- 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)
- 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.

MEDLINE search strategy

The MEDLINE search strategy was translated for use in the other sources.

1 Aortic Valve/ 38262
2 Heart Valve Diseases/ 25387
3 exp Aortic Valve Disease/ 62415
4 (aortic* adj4 (insufficient* or narrow* or stenos* or incompetenc* or regurgitat* or disease* or aneurysm)).tw. 62048
5 Endocarditis, Bacterial/ 20359
6 ((infect* or bacterial*) adj4 endocarditis).tw. 18473
7 or/1-6 153840
8 Heart Valve Prosthesis/ 39516
9 Heart Valve Prosthesis Implantation/ 26536

10 (valve adj4 (neocuspidi?ation or neo-cuspidi?ation or reconstruct* or repair* or replace*)).tw. 43778
11 or/8-10 73739
12 7 and 11 44074
13 Pericardium/ 16775
14 (pericardium or pericardial or epicardium).tw. 34383
15 13 or 14 41386
16 12 and 15 1867
17 Glutaral/ 7236
18 glutaraldehyde*.tw. 16055
19 17 or 18 18317
20 16 and 19 192
21 ((Ozaki* adj4 (sizer or procedure* or technique*)) or AVNEO or (aortic adj4 valve adj4 neocuspidization) or xAVNEO or (xenologous adj4 AVNEO)).tw. 86
22 Ozaki*.tw. 176
23 22 and 7 62
24 20 or 21 or 23 261
25 Animals/ not Humans/ 5023025
26 24 not 25 220

Other relevant studies

Other potentially relevant studies to the IP overview that were not included in the main evidence summary (tables 2 and 3) are listed in table 5.

Table 5 additional studies identified

Article	Number of patients and follow up	Direction of conclusions	Reason study was not included in main evidence summary
Akiyama S, Iida Y, Kazuma S et al. (2020) Midterm outcome of aortic valve neocuspidization for aortic valve stenosis with small annulus. General thoracic and cardiovascular surgery. 68(8): 762-767	Case series n=34 Mean follow-up period: 28.0 ± 22.7 months	The midterm outcome of AVNeo for AS with a small annulus was excellent. The long-term outcome and reliability of this procedure must be fully clarified.	The number of patients is less than 50. Studies with more patients or longer follow up are included.
Amabile A, Krane M, Dufendach K et al. (2022) Standardized Aortic Valve Neocuspidization for Treatment of Aortic Valve Diseases. The Annals of thoracic surgery. 114(4): 1108-1117	Literature review n=1372 (10 studies)	Aortic valve neocuspidization is a versatile and standardized alternative to aortic valve replacement with a biological prosthesis. Early to midterm outcomes from a number of centers are excellent and demonstrate the safety and durability of the procedure. Long-term outcomes and clinical trial data are necessary to determine which patients benefit the most from this procedure	A more recent systematic review and meta-analysis is included.

Arutyunyan V, Chernov I, Komarov R et al. (2020) Immediate Outcomes of Aortic Valve Neocuspidization with Glutaraldehyde-treated Autologous Pericardium: a Multicenter Study.Brazilian journal of cardiovascular surgery.35:241-248	Prospective multicentre study n= 170 Followed during hospital stay	AVNeo is feasible and reproducible with good clinical results. Hemodynamically, AVNeo produces immediate postoperative low-pressure gradients, large EOA, and minimal regurgitation of the aortic valve. Further studies are necessary to evaluate mid- and long-term evolution.	Studies with more patients or longer follow up are included. Study is included in the meta-analysis by Mylonas et al. (2023)
Baird C, Cooney B, Chavez M et al. (2021) Congenital aortic and truncal valve reconstruction using the Ozaki technique: Short-term clinical results. The journal of thoracic and cardiovascular surgery.161: 1567-1577	Retrospective analysis n=57 Median follow-up of 8.1 months	The aortic valve reconstruction procedure has acceptable short-term results and should be considered for valve reconstruction in pediatric patients with congenital aortic and truncal valve disease. Longer-term follow-up is necessary to determine the optimal patch material and late valve function and continued annular growth.	Studies with more patients or longer follow up are included. Study is included in the meta-analysis by Mylonas et al. (2023)
Chan J, Basu A, Di Scenza G et al. (2022) Understanding aortic valve repair through Ozaki procedure: A review of literature evidence. Journal of Cardiac Surgery. 1-5	Literature review n= 1342 (9 studies)	AVNeo can be a suitable alternative to surgical aortic valve replacement in selected patients. The short- and midterm outcomes are comparable without the need for long-term oral anticoagulation. Long-term follow-up data are required for this novel approach to be widely adopted.	A more recent systematic review and meta-analysis is included.

Chan J, Rahman-Haley S, Mittal T et al. (2011) Truly stentless autologous pericardial aortic valve replacement: an alternative to standard aortic valve replacement. The journal of thoracic and cardiovascular surgery. 141(1):276-83	Case series n=11 Mean follow-up was 6.5 years (range, 5.3−7.5 years).	Truly stentless aortic valve replacement using autologous pericardium sutured directly onto the aortic wall is safe and feasible and has excellent durability up to 7.5 years with no calcification.	The number of patients is less than 50. Studies with more patients or longer follow up are included.
Chivers S, Pavy C, Vaja R et al (2019) The Ozaki Procedure With CardioCel Patch for Children and Young Adults With Aortic Valve Disease: Preliminary Experience - a Word of Caution. World journal for pediatric & congenital heart surgery;10(6):724-730	Case series n=5 Mean follow-up: 29.6 months (range: 22-36 months)	Ozaki procedure with CardioCel in pediatric and young adult patients should be approached with caution. Further research with larger groups of pediatric patients, comparison of different graft materials, and longer follow-up is required to ascertain long-term success in children.	The number of patients is less than 50. Studies with more patients or longer follow up are included. Study is included in the meta-analysis by Mylonas et al. (2023)
Duran C M, Gometza B, Kumar N et al. (1995) Aortic valve replacement with freehand autologous pericardium. The journal of thoracic and cardiovascular surgery. 110(2):511-6	Case series n=51 Mean follow-up: 21.2 months	The results obtained so far encourage us to continue replacing the aortic valve with stentless autologous pericardium	Studies with more patients or longer follow up are included.
Iida Y, Fujii S, Akiyama S et al. (2018) Early and mid-term results of	Case series n=57	AVNeo is suitable for patients with AS considering its early and mid-term outcomes.	Studies with more patients or longer follow

isolated aortic valve neocuspidization in patients with aortic stenosis. General thoracic and cardiovascular surgery. 66(11): 648-652	The mean follow-up period was 30.4 ± 20.8 months	Verification of long-term outcomes and reliability is necessary	up are included. Study is included in the meta-analysis by Mylonas et al. (2023) and Benedetto et al. (2021)
Iida Y, Sawa S, Fujii S et al. (2020) Aortic valve neocuspidization in patients under 65 years old. General thoracic and cardiovascular surgery. 68(8):780-784	Case series n=36 The mean follow-up period was 47.8 ± 27.3 months	AVNeo in patients aged under 65 years appears to be suitable considering its early and midterm outcomes. Verification and follow-up of its long-term outcomes and reliability are indispensable.	The number of patients is less than 50. Studies with more patients or longer follow up are included. Study is included in the meta-analysis by Benedetto et al. (2021)
Kasimir M, Simon P, Seebacher G et al. (2004) Reconstructed bicuspid aortic valve after 10 years: clinical and echocardiographic follow-up. The heart surgery forum. 7(5):e485-9	Case series n=13 Long-term follow-up (mean, 10.06 ± 1.01 years)	In contrast to early follow-up results of 5 reoperations, clinical and echocardiographic results were excellent for 10 patients who had undergone reconstruction of bicuspid incompetent aortic valves, and the patients were in stable condition after 10 years. However, the mode of early failure is unknown. Reconstruction of bicuspid valves is possible in selected patients.	The number of patients is less than 50. Studies with more patients or longer follow up are included.
Kawase I, Ozaki S, Yamashita H et al (2013) Aortic valve reconstruction with autologous pericardium for dialysis patients.	Case series n=54 Mean follow up: 847 days	Medium-term results are excellent. Since warfarin for dialysis patients becomes problematic, a postoperative warfarin-free status is desirable.	Studies with more patients or longer follow up are included. Study is included in the

Interactive cardiovascular and thoracic surgery. 16(6):738-42		Aortic valve reconstruction can provide patients with a better quality of life without warfarin	systematic review by Dilawar et al. (2022)
Kawase I, Ozaki S, Yamashita H et al. (2012) Aortic valve reconstruction of unicuspid aortic valve by tricuspidization using autologous pericardium. The Annals of thoracic surgery. 94(4):1180-4)	Case series n=9 Mean follow up: 551.1 days	Diseased unicuspid aortic valves were treated by our original aortic valve reconstruction technique with excellent early results. We continue to study the long-term results.	The number of patients is less than 50. Studies with more patients or longer follow up are included. Study is included in the systematic review by Dilawar et al. (2022)
Koechlin L, Schurr U, Miazza J et al. (2020) Echocardiographic and Clinical Follow-up After Aortic Valve Neocuspidization Using Autologous Pericardium. World journal of surgery. 44(9):3175-3181	Case series n=35 Median follow up: 645 (430-813) days	The Ozaki procedure is reliable and reoperation due to structural valve deterioration nil within a median 645 days follow-up period. The low rate of moderate aortic regurgitation will be surveilled very closely. Further studies are required to evaluate the significance of this procedure in aortic valve surgery.	The number of patients is less than 50. Studies with more patients or longer follow up are included. Study is included in the meta-analysis by Mylonas et al. (2023) and Benedetto et al. (2021).
Krane M, Boehm J, Prinzing A et al. (2021) Excellent Hemodynamic Performance After Aortic Valve Neocuspidization Using Autologous Pericardium. The Annals of thoracic surgery. 111(1):126-133	Case series n=102 Mean follow-up was 426 ± 270 days.	AVNeo shows low reoperation rates after surgery within the first 2 years. The hemodynamic performance is excellent, and the effective orifice area and MPG remain stable within the first year.	Studies with more patients or longer follow up are included. Study is included in the meta-analysis by Mylonas et al. (2023) and Benedetto et al. (2021) and in the systematic

			review by Dilarwar et al. (2022).
Liu X, Han L, Song Z et al. (2013) Aortic valve replacement with autologous pericardium: long-term follow-up of 15 patients and in vivo histopathological changes of autologous pericardium. Interactive cardiovascular and thoracic surgery. 16(2) 123-8	Case series n=15 The mean clinical follow-up was 11.43 ± 4.50 years.	Autologous pericardial aortic valve (APAV) replacement is a procedure with a low mortality. APAVs adapt to new environmental demands by producing an elastic band and by endothelialization, whereas myofibroblast/osteoblast transdifferentiation seems to be responsible for the fibrocalcification of APAVs.	The number of patients is less than 50. Studies with more patients or longer follow up are included.
Marathe S P, Chavez M, Sleeper L A et al. (2021) Single-Leaflet Aortic Valve Reconstruction Utilizing the Ozaki Technique in Patients With Congenital Aortic Valve Disease. Seminars in Thoracic and Cardiovascular Surgery.	Case series n=33 The median follow-up was 1.1 year	Single-leaflet aortic valve leaflet reconstruction utilizing the Ozaki technique has promising early results and can be considered in patients when there are acceptable native leaflets.	The number of patients is less than 50. Studies with more patients or longer follow up are included.
Marathe S P, Chavez M, Sleeper L et al. Modified Ozaki Procedure Including Annular Enlargement for Small Aortic Annuli in Young Patients.The Annals of thoracic surgery. 110(4):1364-1371	Case series n=51 Mean follow-up of 11.9 months	The Ozaki procedure has acceptable short-term results in young patients with small aortic annuli. A larger aortic annulus can be achieved with surgical annular enlargement. Long-term follow-up is necessary to determine late valve function and potential continued annular growth	Studies with more patients or longer follow up are included.

Makino M, Yamamoto H, Ishibashi-Ueda H et al. (2019),A case of aortic valve leaflet tear and perforations after neocuspidization. ESC Heart Failure. 6: 446-448	Case report n=1 27 months after AVNeo	Encountered a first case of AV leaflet tear and perforations 27 months after AVNeo using autologous pericardium	Studies with more patients or longer follow up are included.
Mittal C, Sachin T, Velayoudham D et al. (2009) Early results of aortic valve reconstruction with stentless glutaraldehyde treated autologous pericardial valve. Indian J Thorac Cardiovasc Surg 25: 178–182	Retrospective n=34 Mean follow up: 16.3 ± 8.6 months	Aortic Valve reconstruction using glutaraldehyde treated autologous pericardium is feasible in young patients with acceptable results.	The number of patients is less than 50. Studies with more patients or longer follow up are included. Study is included in the systematic review by Dilawar et al. (2022).
Mourad F, Shehada S, Lubarski J et al. (2019) Aortic valve construction using pericardial tissue: short-term single-centre outcomes. nteractive cardiovascular and thoracic surgery. 28(2) 183-190	Prospective single-centre study n=52 Mean follow-up: 11.2 ± 4.8 month	Aortic valve construction using pericardial tissue could be an alternative in middle-age patients presenting with aortic valve disease in whom valve repair was not possible. The newly designed templates allow exact sizing of the neo-cusps and optimal commissure implantation; however, long-term follow-up in a larger cohort is warranted to assess the durability of the neo-valves.	Studies with more patients or longer follow up are included. Study is included in the meta-analysis by Mylonas et al. (2023) and Benedetto et al. (2021).
Ngo H T, Nguyen H C, Thinh D et al. (2022) Aortic valve reconstruction surgery using	Case series n=72 The mean follow-up time was 26.4	This procedure was safe and effective, with favorable valvular hemodynamics and a low rate of valvular	Studies with more patients or longer follow

autologous pericardium: The experience in Vietnam. Journal of cardiac surgery. 37(5): 1233-1239	months (12-42 months)	degeneration. However, more long-term follow-up data are needed	up are included.
Ngo H T, Nguyen H C, Nguyen T T et al. Reconstruction of aortic valve by autologous pericardium (Ozaki's procedure): Single center experience in Vietnam. Asian cardiovascular & thoracic annalsAsian cardiovascular & thoracic annals. 29(5):394-399	Case series n=61 The mean follow-up period was 18.5 ± 5.7 months	Aortic valve reconstruction with autologous pericardium provided good outcomes in our study.	Studies with more patients or longer follow up are included. Study is included in the meta-analysis by Mylonas et al. (2023), and in the systematic review by Dilarwar et al. (2022).
Nguyen D H, Vo A T, Le K et al. (2018) Minimally Invasive Ozaki Procedure in Aortic Valve Disease: The Preliminary Results. Innovations (Philadelphia, Pa.). 13(5) 332-337	Case series n=9 NA	Ministernotomy combined with Ozaki procedure might be feasible, as well as an alternative to conventional sternotomy. This approach is associated with low mortality and morbidity and may be beneficial in younger populations.	The number of patients is less than 50. Studies with more patients or longer follow up are included. Study is included in the meta-analysis by Mylonas et al. (2023).
Nguyen T, Vo A, Nguyen D et al. (2020). Progressive Left Ventricular Hypertrophy After Ozaki Procedure: A Case Report. The Heart Surgury Forum. 23(6)	Case report n=1 NA	A 57-year-old man with symptomatic severe aortic stenosis who underwent Ozaki technique Ozaki procedure. Seven months later, he rapidly developed progressive left ventricular hypertrophy with a left ventricular	Studies with more patients or longer follow up are included.

		outflow tract obstruction. This required a reoperation for septal myectomy.	
Ozaki S, Kawase I, Yamashita H et al. (2018) Midterm outcomes after aortic valve neocuspidization with glutaraldehyde-treated autologous pericardium. The Journal of thoracic and cardiovascular surgery. 155(6) 2379-2387	Case series n=850 he mean follow-up period was 53.7 ± 28.2 months	The midterm outcomes of AVNeo using autologous pericardium were satisfactory in 850 patients with various aortic valve diseases. However, further randomized, multicenter prospective studies are needed to confirm the results of the current study	Study is included in the meta-analysis by Mylonas et al. (2023) and Benedetto et al. (2021) and in the systematic review by Dilarwar et al. (2022).
Ozaki S, Kawase I, Yamashita H et al. (2014) Reconstruction of bicuspid aortic valve with autologous pericardium--usefulness of tricuspidization. Circulation journal: official journal of the Japanese Circulation Society. 78(5) 1144-51	Case series n=34 Mean follow-up was 733 days	Medium-term results were excellent. Tricuspidization gave good opening and closure of aortic valve with excellent hemodynamics.	The number of patients is less than 50. Studies with more patients or longer follow up are included. Study is included in the systematic review by Dilawar et al. (2022).
Ozaki S, Kawase I, Yamashita H et al. (2014) A total of 404 cases of aortic valve reconstruction with glutaraldehyde-treated autologous pericardium. The Journal of thoracic and cardiovascular surgery. 147(1) 301-6	Retrospective study n=404 The mean follow-up period was 23.7 ± 13.1 months.	Original aortic valve reconstruction was feasible in patients with various aortic valve diseases. Long-term data will be disclosed in the future.	Study is included in the systematic review by Dilawar et al. (2022).
Ozaki S, Kawase I, Yamashita H et al.	Case series	AVP provides good short- and mid-term	Studies with more patients

(2011) Aortic valve reconstruction using self-developed aortic valve plasty system in aortic valve disease. Interactive cardiovascular and thoracic surgery. 12(4) 550-3	n=88 One year follow-up echocardiography	results with good hemodynamics and good quality-of-life without anticoagulation. This procedure is effective especially for calcified AS with small aortic annulus in elderly patients. Assessment of long-term data especially regarding valve durability will be examined in the future.	or longer follow up are included.
Pirola S, Mastroiacovo G, Arlati F et al. (2020) Single center 5-years' experience of Ozaki procedure: mid-term follow-up. The Annals of thoracic surgery. 111(6):1937-1943	Retrospective study n=71 The median follow-up period was 20.7 months (range, 2 to 47)	Midterm outcome follow-up of the Ozaki procedure showed optimal results in terms of mortality, transaortic valve gradients, freedom from major adverse valve-related events, and recurrence of aortic valve insufficiency. Visual Abstract	Studies with more patients or longer follow up are included. Study is included in the meta-analysis by Mylonas et al. (2023) and Benedetto et al. (2021).
Pirola S, Mastroiacovo G, Giorgio A et al. (2021) Single Center Five Years' Experience of Ozaki Procedure: Midterm Follow-up. The Annals of thoracic surgery. 111(6):1937-1943	Retrospective study n=71 The median follow-up period was 20.7 months (range, 2 to 47)	Midterm outcome follow-up of the Ozaki procedure showed optimal results in terms of mortality, transaortic valve gradients, freedom from major adverse valve-related events, and recurrence of aortic valve insufficiency.	Studies with more patients or longer follow up are included.
Polito A, Albanese S B, Cetrano E et al. (2021) Aortic valve neocuspidalization in paediatric patients with isolated aortic valve disease: early experience. Interactive cardiovascular and	Case series n=22 Median follow-up of 11.3 (4.7-21) months	The Ozaki procedure is safe and effective in paediatric patients with aortic valve disease. The use of heterologous pericardium should probably be minimized. Moreover, preoperative small aortic annuli should probably be promptly treated by means of an associated	The number of patients is less than 50. Study is included in the meta-analysis by Mylonas et al. (2023).

thoracic surgery. 32(1):111-117		ring enlargement procedure	
Polito A, Albanese S, Cetrano E et al. (2021) Aortic Valve Neocuspidalization May Be a Viable Alternative to Ross Operation in Pediatric Patients. Pediatric cardiology. 42(3):668-675	Comparative study n=38 Median follow-up of 18.2 (5-32) months	The medium-term outcome of Ozaki and Ross in paediatric patients is similar, despite an increased tendency of the former to develop aortic transvalvular gradient in the follow-up. Future larger multicenter studies with longer follow-up are warranted to confirm these results.	The number of patients is less than 50.
Prinzing A, Bohm J, Sideris K et al. (2022) AVNeo Improves Early Hemodynamics In Regurgitant Bicuspid Aortic Valves Compared To Aortic Valve Repair. Interactive cardiovascular and thoracic surgery. 35(5)	Retrospective study n=22 NA	Compared to AV-repair, patients AVNeo showed lower MPGs and larger orifice areas at discharge. The functional result was not different.	The number of patients is less than 50.
Reuthebuch O, Koechlin L, Schurr U et al. (2018) Aortic valve replacement using autologous pericardium: single centre experience with the Ozaki technique. Swiss medical weekly. 148:	Retrospective study n=30 Mean follow-up: 3 months	In our experience, it can be mastered after a relatively short training period, and has become part of our routine clinical toolbox. The use of autologous pericardium in combination with excellent haemodynamics may have the potential to overcome the structural disadvantages of biological aortic valves, to be beneficial in infective endocarditis, and to represent an alternative for patients with small annuli.	The number of patients is less than 50. Study is included in the systematic review by Dilawar et al. (2022).

Rosseikin E V, Kobzev E E, Bazylev V V. (2019) Minimally invasive Ozaki technique. Angiology and vascular surgery. 25(3) 142-155	Retrospective study n=30 NA	Minimally invasive approach apart from a good cosmetic effect has a series of advantages over full sternotomy by the in-hospital and remote outcomes	The number of patients is less than 50. Study is included in the meta-analysis by Mylonas et al. (2023).
Secinaro A, Milano E G, Ciancarella P et al. (2022) Blood flow characteristics after aortic valve neocuspidization in paediatric patients: a comparison with the Ross procedure. European heart journal. Cardiovascular Imaging. 23(2):275-282	Prospective cohort n=20 NA	Proximal aorta flow dynamics of children treated with the Ozaki and the Ross procedure are comparable. Similarly to the Ross, Ozaki technique restores a physiological laminar flow pattern in the short-term follow-up, with the advantage of not inducing a bivalvular disease, although further studies are warranted to evaluate its long-term results.	The number of patients is less than 50. Study is included in the meta-analysis by Mylonas et al. (2023).
Shearn A I U, Ordonez M V, Rapetto F et al. (2020) Rapid Prototyping Flexible Aortic Models Aids Sizing of Valve Leaflets and Planning the Ozaki Repair. JACC: Case Reports. 2(8):1137-1140	Case report n=2 NA	Two patients with bicuspid aortic valve were selected for aortic valve repair using the Ozaki procedure. Patient-specific models of their aortic roots were generated based on computed tomography data and were 3-dimensional printed using a flexible resin.	The number of patients is less than 50. No important adverse events reported.
Sivalingam S, Haranal M, Pathan I, (2022) Aortic valve neocuspidization for aortic regurgitation associated with ventricular septal defect. Interactive	Restrospective review n=7 mean follow-up period was 2.6±0.8 years	The aortic leaflet neocuspidization procedure for the aortic valve is a relatively new concept. Availability of a template makes it an easily reproducible valve repair in paediatric patients with a single-leaflet	The number of patients is less than 50.

cardiovascular and thoracic surgery. 34(2): 315-321		abnormality. This technique preserves the remaining 2 normal leaflets, thus promoting the growth potential while maintaining near normal aortic root complex dynamics.	
Shi T, Gao Z, Li S et al. (2022) Single leaflet reconstruction in paediatric aortic regurgitation using the Ozaki procedure. Cardiology in the young. 32(5) 789-793	Case series n=9 The median follow-up was 22 (14, 33) months	Single leaflet reconstruction using the Ozaki procedure was an effective surgical method for treating children with aortic regurgitation in our centre with satisfactory short-term results.	The number of patients is less than 50. Study is included in the meta-analysis by Mylonas et al. (2023).
Vijayan J, Lachma R, Rao P et al. (2019) Autologous pericardial aortic valve reconstruction: early results and comparison with mechanical valve replacement. Indian Journal of Thoracic and Cardiovascular Surgery. 36(3):186-192	Prospective cohort n=20 NA	Autologous pericardial aortic valve reconstruction is a feasible alternative to prosthetic valve replacement with several advantages.	The number of patients is less than 50. Study is included in the meta-analysis by Mylonas et al. (2023).
Watanabe F, Go K, Kojima T (2021) Valvular changes after aortic valve neo-cuspidization in children: A case series. Pediatrics international : official journal of the Japan Pediatric Society. 63(11):1289-1296	Case series n=7 Postoperative transthoracic echocardiography 3 months after the procedure	Most cases exhibited spontaneous improvement in AR, while one developed postoperative AS. Further prospective investigation is, therefore, needed to explore surgical outcomes following AVNeo among children.	The number of patients is less than 50. Study is included in the meta-analysis by Mylonas et al. (2023).

Wiggins L M, Mimic B, Issitt R et al. (2020) The utility of aortic valve leaflet reconstruction techniques in children and young adults. The Journal of thoracic and cardiovascular surgery. 159(6):2369-2378	Case series n=40 A median echocardiographic follow-up of 14.1 months (7.2-20.1 months)	Aortic leaflet reconstruction provides acceptable short-term hemodynamic outcomes and proves the utility of this technique as an adjunctive strategy for surgical treatment of aortic valve disease in children and young adults.	The number of patients is less than 50. Study is included in the meta-analysis by Mylonas et al. (2023).
Yamamoto Y, Iino K, Shintani Y et al. (2017) Comparison of Aortic Annulus Dimension After Aortic Valve Neocuspidization With Valve Replacement and Normal Valve. Seminars in thoracic and cardiovascular surgery. 29(2):143-149	Retrospective cohort n=8 NA	e results of the present study demonstrated that aortic annular dimensions after AVNeo are similar to the dimensions of normal aortic valves.	The number of patients is less than 50. Study is included in the meta-analysis by Mylonas et al. (2023).