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REVIEW

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Aortic valve neocuspidization with autologous pericardium in adult patients: UK experience and meta-analytic comparison with other aortic valve substitutes

Umberto Benedetto [a,*†], Shubhra Sinha [a,†], Arnaldo Dimagli [a], Lauren Dixon[a], Serban Stoica[a], Lucia Cocomello[a], Cesare Quarto[b], Gianni D. Angelini[a], Uday Dandekar[c,‡] and Massimo Caputo[a,‡]

[a] Bristol Heart Institute, Translational Health Sciences, University of Bristol, Bristol, UK
[b] Department of Cardiothoracic Surgery, Royal Brompton Harefield NHS Trust, London, UK
[c] Department of Cardiothoracic Surgery, University Hospital Coventry Warwickshire NHS Trust, Coventry, West Midlands, UK

* Corresponding author. Bristol Heart Institute, Translational Health Sciences, University of Bristol, Office Room 84, Level 7, Bristol Royal Infirmary, Upper Maudlin Street, Bristol BS2 8HW, UK. Tel: +44-0117-3428854; e-mail: umberto.benedetto@bristol.ac.uk (U. Benedetto).

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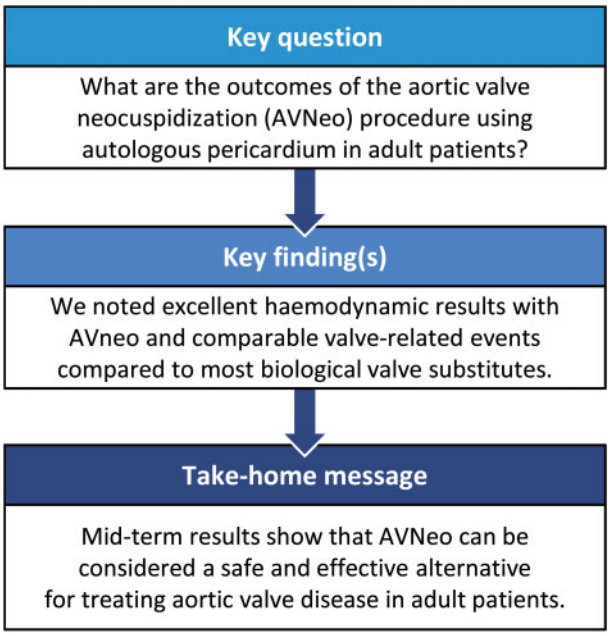

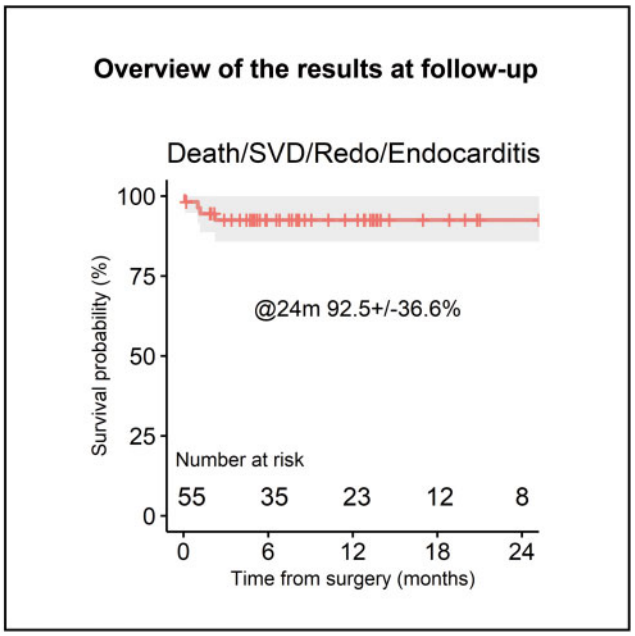

Abstract

OBJECTIVES: We sought to provide further evidence on the safety and efficacy of aortic valve neocuspidization (AVNeo) using autologous pericardium in adult patients with aortic valve disease by reporting clinical and echocardiographic results from the first UK experience and performing a meta-analytic comparison with other biological valve substitutes.

†The first two authors have equal contribution on the paper.
‡The last two authors have equal seniority on the paper.

METHODS: We reported clinical and echocardiographic outcomes of 55 patients (mean age 58 ± 15 years) undergoing AVNeo with autologous pericardium in 2 UK centres from 2018 to 2020. These results were included in a meta-analytic comparison between series on AVNeo (7 studies, 1205 patients, mean weighted follow-up 3.6 years) versus Trifecta (10 studies, 8705 patients, 3.8 years), Magna Ease (3 studies, 3137 patients, 4.1 years), Freedom Solo (4 studies, 1869 patients, 4.4 years), Freestyle (4 studies, 4307 patients, 7 years), Mitroflow (4 studies, 4760 patients, 4.1 years) and autograft aortic valve (7 papers, 3839 patients, 9.1 years).

RESULTS: In the present series no patients required intraoperative conversion. After mean follow-up of 12.5 ± 0.9 months, 3 patients presented with endocarditis and 1 required reintervention. The remaining patients had absent or mild aortic valve insufficiency with very low peak and mean transvalvular gradients (16 ± 3.7 and 9 ± 2.2 mmHg, respectively). Meta-analytic estimates showed non-significant difference between AVNeo and all but Magna Ease valves with regards to structural valve degeneration, reintervention and endocarditis. When compared Magna Ease valve, AVNeo and other valve substitutes showed an excess of valve-related events.

CONCLUSIONS: AVNeo is safe, associated with excellent haemodynamic profile. Its midterm risk of valve-related events is comparable to most biological valve substitutes. Magna Ease is potentially the best biological choice as far as risk of reintervention is concerned.

Keywords: Ozaki • Aortic valve neocuspidization • Aortic valve neocuspidization • Aortic valve

ABBREVIATIONS

AI	Aortic insufficiency
AV	Aortic valve
AVNeo	Aortic valve neocuspidization
AVR	AV replacement
MWFU	Mean weighted follow-up
NYHA	New York Heart Association
SVD	Structural valve degeneration
TAVI	Transcatheter aortic valve implantation
TOE	Transoesophageal echocardiography

INTRODUCTION

Aortic valve neocuspidization (AVNeo) with autologous pericardium is emerging as an attractive option, which can be applied to a wide spectrum of aortic valve (AV) diseases [1–6]. This technique provides a biocompatible treatment that avoids the need for anticoagulation [1]. This method provides maximal effective orifice area as no sewing ring is needed thus translating into low transvalvular gradients [3, 7]. Moreover, a new technique introduced by Ozaki *et al.* [1, 7] based on special templates and a different sizing concept has made AVNeo more reproducible with promising mid- to long-term results.

Despite this, AVNeo is currently performed in a limited numbers of adults, and it remains a technique mostly adopted in paediatric patients [8, 9]. The slow adoption of AVNeo in adults is partially determined by the scarcity of available data except from the original series reported by Ozaki *et al.* [1, 2, 7]. More importantly, concerns remain on the increased risk of valve failure with AVNeo when compared to conventional bioprosthetic valves, as comparison between these is still lacking.

We sought to provide further evidence on the safety and efficacy of AVNeo procedure using autologous pericardium in adults by reporting clinical and echocardiographic results from the first UK experience and by performing a meta-analytic comparison with other biological substitutes, including biological valve substitutes and aortic autograft (Ross procedure).

METHODS

The present study included 2 separate analyses. Firstly, we reported on the first UK experience on adult patients treated with AVNeo using autologous pericardium. These results were subsequently pooled with other available series to perform a meta-analytic comparison with other biological substitutes.

First experience of using AVNeo in UK adult patients

This analysis was approved by the local audit committee and was in accordance with the principles of the Declaration of Helsinki. All authors had unlimited access to the complete data set and had taken responsibility for its integrity. All authors have read and agreed to the manuscript. In the UK, University Hospitals Bristol NHS Foundation Trust and University Hospital Coventry & Warwickshire have started performing AVNeo using autologous pericardium in adult patients (>18 years old) since 2018. AVNeo has been performed by 3 surgeons (2 in Bristol and 1 in Coventry). Perioperative and follow-up data were prospectively collected as part of an institutional audit. All patients underwent intraoperative transoesophageal echocardiography (TOE) assessment before and after AVNeo. After discharge, they were regularly seen as outpatients and underwent annual echocardiograms. Aortic insufficiency (AI) was graded as follows: 0 = absent, 1 = mild, 2 = mild-to-moderate, 3 = moderate and 4 = severe. Echocardiographic criteria for structural valve degeneration (SVD) were as follows: (i) mean gradient > 40 mmHg or (ii) AI of grade 3 or 4. The composite of death, reintervention, endocarditis on the AV or the incidence of SVD at the latest follow-up available was considered the primary end point. Other outcomes of interest were (i) intraoperative results including conversion to AV replacement (AVR) with a prosthetic valve, rate and type of combined procedure, cross-clamp and cardiopulmonary bypass time, results of post-operative TOE assessment and (ii) in-hospital complications (i.e. stroke, myocardial infarction, re-exploration for bleeding, dialysis and in-hospital mortality).

Surgical technique

All adult patients with AV disease are potentially eligible for an AVNeo procedure. However, AVNeo was more likely to be offered as an alternative to biological prosthetic valve in young patients who have contraindication or want to avoid lifelong anticoagulation for mechanical prosthetic valve. The decision whether to use AVNeo procedure was extensively discussed

Table 1: Baseline characteristics of patients undergoing AVNeo in UK series

Number of patients	55
Number of patients in each year, *n* (%)	
2018	11 (20)
2019	19 (35)
2020	25 (46)
Number of patients operated on per surgeon, *n* (%)	
Surgeon #1	30 (55)
Surgeon #2	14 (26)
Surgeon #3	11 (20)
Age (years), mean (SD)	57.99 (15.03)
Male, *n* (%)	34 (62)
Preoperative NYHA, *n* (%)	
1	10 (18)
2	19 (34)
3	23 (42)
4	3 (6)
Endocarditis, *n* (%)	8 (15)
Morphology, *n* (%)	
Bicuspid	30 (55)
Tricuspid	25 (46)
LVEF, *n* (%)	
Good	45 (82)
Moderate	9 (16)
Severe	1 (2)
Combined procedure, *n* (%)	23 (42)
Type of combined procedure, *n* (%)	
Ascending	11 (20)
CABG	8 (15)
Excision of subaortic membrane and accessory tissue on AMVL	1 (2)
MV repair	3 (6)
CPB time, median (IQR)	136.0 (114.5–166.0)
Cross-clamp time, median (IQR)	108.0 (95.0–131.5)
Conversion to AVR, *n* (%)	0 (0)
Postoperative TOE AI, *n* (%)	
None	39 (71)
Present	16 (29)

AI: aortic insufficiency; AMVL: anterior mitral valve leaflet; AVNeo: aortic valve neocuspidization; AVR: aortic valve replacement; CABG: coronary artery bypass grafting; CPB: cardiopulmonary bypass; IQR: interquartile range; LVEF: left ventricular ejection fraction; MV: mitral valve; NYHA: New York Heart Association functional class; SD: standard deviation; TOE: transoesophageal echocardiography.

with the patient and referring cardiologist preoperatively. Contraindications to AVNeo with autologous pericardium were previous thoracic irradiation, evidence of pericarditis and previous sternotomy due to the potential damage to the pericardium. The operative technique has already been described by Ozaki *et al.* [1]. In brief, after median sternotomy, the pericardium was dissected and treated for 10 min with a 0.6% glutaraldehyde solution prior to being rinsed 3 times for 6 min with sterile saline. In the meantime, the ascending aorta and the right atrium were cannulated, and cardiopulmonary bypass was established. Cardioplegic arrest was accomplished with blood cardioplegia in all cases. After aortotomy, the diseased cusps were resected. The distance between each commissure was measured using a special measuring device. The pericardium was subsequently cut according to a template that corresponded to the measured size. The inner side of the pericardium (serous lamina) is smoother and therefore this side faces the ventricle. The cusps were then sewn along the annuli with a 4–0 running suture, and commissural coaptation was secured with additional 4–0 sutures. All sutures were knotted and reinforced with a Teflon patch on the outside of the aorta. The functionality of the substituted valve was assessed intraoperatively with water testing and postoperatively by TOE. No pericardial patch was used to replace the removed pericardium. Postoperatively, lifelong antiplatelet therapy was prescribed (150 mg aspirin per day).

Statistical analysis

Data were presented as frequency and percentage for categorical variables and as mean and standard deviation for continuous variables. New York Heart Association (NYHA) class of the patients preoperatively and postoperatively were compared using the Wilcoxon signed-rank test. For time to event data (i.e. freedom from death, reintervention or SVD), Kaplan–Meier estimates and relative standard error were calculated. Changes in echocardiographic measurements overtime (i.e. valve insufficiency of transvalvular systolic gradients) were analysed as longitudinal data using a mixed linear model (lme4 package, https://cran.r-project.org/package=lme4). Individual subjects were used as random effect (intercept). Time to echocardiographic follow-up was forced as explanatory variable. Clustering effect due to different time points of follow-up was also investigated (random slope).

Meta-analysis

Systematic review of series on AVNeo procedure and AVR using other biological substitutes followed the PRISMA statement principle. We screened citations from MEDLINE (1966–October 2019), CINAHL (1981–October 2019), EMBASE (1980–October 2019) and EMCARE (1946–October 2019). The search strategy is presented in Supplementary Material. For studies reporting on AVNeo, we included those which reported specifically on procedures performed with autologous pericardium in adult patients (>18 years) with follow-up data available. Case report, articles reporting on surgical technique and AVNeo series on paediatric population (<18 years) were excluded. For the comparison with other biological substitutes, we selected *a priori* 3 third generation stented xenografts (i.e. Magna Ease, Trifecta and Mitroflow), 2 stentless bioprostheses (i.e. Freedom Solo and Trifecta) and aortic autograft (Ross procedure).

For data on other biological valve substitutes, we prespecified that only studies reporting minimum 500 patients with at least 24-month follow-up were included, except for studies reporting on autografts and Freedom Solo for which the threshold was set at 200 patients. The search strategy is available in the Supplementary Material. The reviewers screened reference lists of included studies. The search is updated to 15 September 2020. All papers were independently screened by 3 reviewers (A.D., L.D. and S.S.); conflicts were resolved by 2 reviewers (U.B. and L.C.). In case of studies with overlapping populations, we predetermined that the study with the largest sample was to be selected. Risk of bias in individual studies was assessed using the quality in prognostic studies instrument as per published protocol [10].

As the majority of studies reported on a single biological valve substitute, network meta-analysis (i.e. direct and indirect evidence) could not be performed [11]. We therefore obtained pooled estimates for each valve and we performed a head to

Table 2: In-hospital outcomes and follow-up data of patients undergoing AVNeo in UK series

n	55
In-hospital	
Postoperative stroke, *n* (%)	0 (0)
Postoperative MI, *n* (%)	0 (0)
Postoperative dialysis, *n* (%)	0 (0)
Reintubation, *n* (%)	1 (7)
Hospital death, *n* (%)	1 (2)
ITU stay (days), mean (SD)	5 (5.03)
LOS (days), mean (SD)	10.93 (8)
Time to follow-up (months), mean (SD)	12.51 (9)
Follow-up outcomes	
Death	1 (2)
Reintervention	1 (2)
Endocarditis	3 (5)
Postoperative NYHA	
1	51 (94)
2	1 (2)
3	2 (4)
4	0 (0)
Last echocardiogram	
Degree of AI	
Nil	43 (78)
Mild	8 (15)
Mild to moderate	4 (7)
Max gradient, mean (SD)	16.3 (6.95)
Mean gradient, mean (SD)	9.2 (4.68)

AI: aortic insufficiency; AVNeo: aortic valve neocuspidization; ITU: intensive therapy unit; LOS: length of stay; MI: myocardial infarction; NYHA: New York Heart Association functional class; SD: standard deviation.

head comparison of pooled estimates for each outcomes of interest. Two separate sets of meta-analytic comparisons were performed. The first set was performed using AVNeo as a reference substitute. The second set was performed using the best valve substitute (i.e. Magna Ease) as the reference substitute. Outcomes of interest were the incidence of SVD, endocarditis and reintervention. We accounted for different follow-up durations using a Poisson model and reporting the number of events observed per total number patient-years. A variance stabilizing transformation (square root) was preferred and performed better than the untransformed methods or methods using canonical logit transformation due to rare events. Pooled meta-analytic estimates for each substitute were obtained using inverse variance method with a random effect model. Estimates based on a fixed effect model were also reported. Pooled meta-analytic estimates were compared using test for subgroup differences as described by described by Borenstein *et al.* [12]. Meta-analytic results were displayed using forest plot (https://cran.r-project.org/web/packages/forestplot/index.html). The presence of small-study effects was verified by visual inspection of the funnel plot and tested by fitting a regression directly to the data using the treatment effect as the dependent variable and standard error as the independent variable. Hypothesis of statistical heterogeneity was tested by means of Cochrane *Q* test, and extent of statistical consistency was measured with I^2, defined as 100% $\times$ $(Q - df)/Q$, where *Q* is Cochran's heterogeneity statistic and *df* (degrees of freedom). This describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance). I^2 value $\geq$75% indicated considerable heterogeneity.

RESULTS

UK AVNeo series

A total of 55 patients were operated on in the 2 UK centres from January 2018 to July 2020. Table 1 provides an overview of baseline characteristics and operative data. Mean age was 58 ± 15 years and 34 (61.8%) were males. The most common indication was calcified aortic stenosis followed by AV endocarditis and only 4 patients had AI. A total of 30 patients had a bicuspid AV. Intraoperatively, there were no conversions to prosthetic valve replacement. Intraoperative TOE showed absent (39, 71%) or mild AI (16, 29%). Post-operative data are summarized in Table 2. Post-operative course was uneventful for all but an 80-year-old patient who developed pneumonia, respiratory failure and later died of sepsis. Mean time to follow-up was 12.5 ± 0.9 months. No patient died post-discharge. 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). Overall, freedom from death, endocarditis, reintervention and SVD was 92.5%± 3.6% (Fig. 1A). At echocardiographic follow-up, no patient presented with SVD and all patients showed absent or mild AI (Fig. 1B) and very low peak and mean transvalvular gradients (16 ± 3.7 and 9 ± 2.2 mmHg, respectively; Fig. 1C), which were stable during follow-up. There was a significant improvement in NYHA class compared to baseline with all but 2patients in class NYHA I–II (Fig. 1D; $P < 0.001$). An overview of clinical and echocardiographic outcomes is presented in Fig. 1 and Supplementary Material, Fig. S1.

Meta-analysis

Search results for full-text articles used for the quantitative and qualitative analyses are reported in Supplementary Material, Fig. S2. Overview of studies included is reported in Table 3. A total number of 7 studies reporting on AVNeo with autologous pericardium were identified including a total of 1204 patients (Supplementary Material, Tables S1 and S2). With the addition of the present study, a total of 1259 patients with AVNeo were available for meta-analysis.

Other biological valve substitutes included for comparison were Trifecta [10 studies, 8705 patients, mean weighted follow-up (MWFU) 3.8 years], Magna Ease (3 studies, 3137 patients, MWFU 4.1 years), Freedom Solo (4 studies, 1869 patients, MWFU 4.4 years), Freestyle (4 studies, 4307 patients, MWFU 7 years), Mitroflow (4 studies, 4760 patients, MWFU 4.1 years) and autograft AV (7 papers, 3839 patients, MWFU 9.1 years) [2–6, 15–23]. No study was found to have high risk of bias (Supplementary Material, Table S3). Study characteristics are reported in Table 3.

Meta-analytic estimates for SVD, endocarditis and reintervention and relative comparisons are reported in Table 4 and Figs 2–4. AVNeo was associated with an incidence rate of 0.34%, 0.45% and 1.07%/patient-year for SVD, endocarditis and reintervention. When the series by Ozaki was removed, pooled estimates were 0.24%, 0.58% and 0.14%/patient-year for SVD, endocarditis and reoperation. AVNeo showed a similar incidence of valve-related events compared to most valve substitutes included in the analysis. However, compared to Magna Ease, there was a significantly higher incidence of reintervention driven by a trend towards

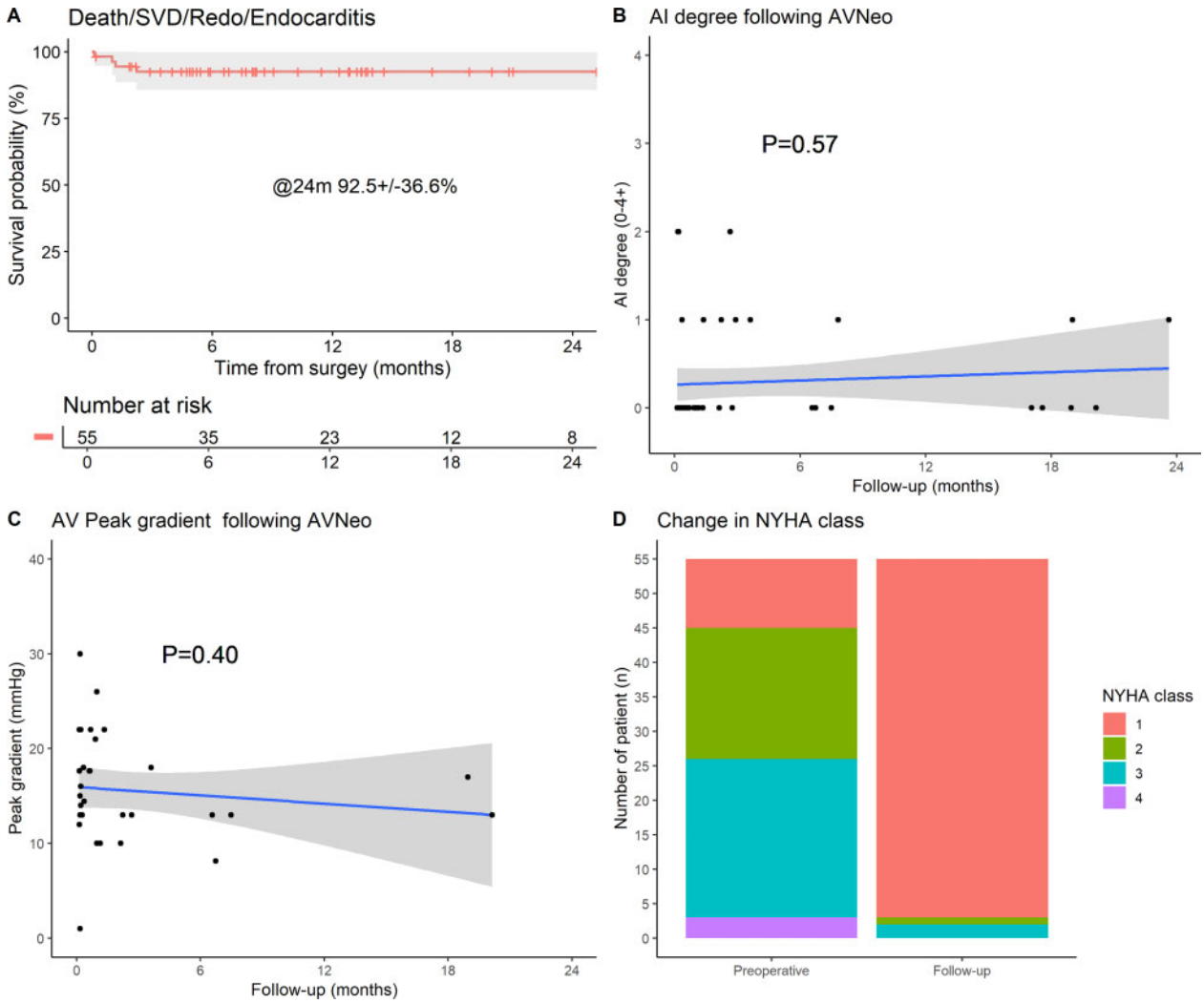

Figure 1: Overview of the results at follow-up. (**A**) Kaplan–Meier freedom from composite of death, SVD, reoperation, endocarditis and after AVNeo. (**B**) Postoperative changes in AI degree during follow-up. (**C**) Postoperative changes in AV peak gradient during follow-up. (**D**) Proportion of patients in each NYHA class before and after aortic AVNeo. AI: aortic insufficiency; AV: aortic valve; AVNeo: aortic valve neocuspidization; NYHA: New York Heart Association; SVD: structural valve degeneration.

an excess incidence of SVD and endocarditis with AVNeo. Magna Ease significantly outperformed other biological valve substitutes in most of the comparisons. No significant statistical evidence of small study effect was found for SVD (Supplementary Material, Fig. S3; $P = 0.26$), endocarditis (Supplementary Material, Fig. S4; $P = 0.23$) reintervention (Supplementary Material, Fig. S5; $P = 0.37$).

DISCUSSION

In this study, we have reported the first UK experience of AVNeo with autologous pericardium in adults with AV disease. Like previous reports, the present findings showed that AVNeo is safe and associated with low surgical morbidity. When our results were pooled with other available series (1259 AVNeo procedures, MWFU 3.6 years), we found that AVNeo was comparable in terms of SVD, endocarditis and reintervention to most biological valve substitutes. However, AVNeo showed a significantly higher incidence of reintervention when compared to Magna Ease Valve driven by a non-significant excess of SVD and endocarditis. In turn, Magna Ease outperformed all AV substitutes in most comparisons.

While AV-sparing surgery is the gold standard for non-degenerative AV disease (i.e. annulectasia) [23], AVR with bioprosthetic or mechanical prosthesis is required for most adults with degenerative or infective AV disease. Mechanical valves present a virtually inexistent risk of SVD but are thrombogenic and require lifelong anticoagulation, which exposes patients to substantial lifetime risks of bleeding or thromboembolism [44], thus increasing the use of bioprostheses in the past decade [45]. Nevertheless, biological AVR in younger patients (<69 years) remains controversial due to accelerated calcific degeneration observed in this group which leads to increased transvalvular gradients, incidence of congestive heart failure, reintervention and mortality [46, 47]. Transcatheter aortic valve implantation (TAVI) represents another biological solution for AV disease but its adoption in younger patients is currently not recommended. There is also a relative contraindication to its use in bicuspid AV, which is associated with suboptimal results after TAVI [48]. AVNeo is effective in tricuspid and bicuspid AVs alike. In case of SVD, AVNeo can be amenable to TAVI [49].

Table 3: Characteristics of studies included in meta-analysis

Author, year	Country	Study period	Study design	Sample size	Age (years), mean (SD)	Male (%)	LVEF (%), mean (SD)	Redo (%)	NYHA 3–4 (%)	BAV (%)	Indication (%)				Combined procedure (%)
											AS	AI	Mixed	IE	
AVNeo															
Ozaki, 2018 [2]	Japan	2007–2015	RS	850	71 (11.9)	52	NR	NR	NR	26.4	62.8	29.9	7.2	2.2	43
Iida, 2018 [3]	Japan	2010–2017	RS	57	78 (8.8)	39	NR	NR	NR	24.6	100	0	0	3.5	0
Iida, 2020 [4]	Japan	2010–2019	RS	36	55 (10.4)	72	NR	NR	NR	30.6	36.1	63.9	0	16.7	0
Koechlin, 2020 [6]	Switzerland	2015–2018	RS	35	72 (12.6)	69	60	NR	15	23	28.6	37.1	34.3	3	43
Mourad, 2018 [5][a]	Germany	2015–2017	RS	52	60 (14.0)	64	NR	NR	90.4	38.5	38.5	26.9	25	9.6	65
Krane, 2020 [13]	Germany	2016–2019	RS	103	54 (16.4)	66	NR	NR	NR	78.6	77.7	22.3	NR	NR	38.9
Pirola, 2020 [14]	Italy	2014–2020	RS	71	52 (14.2)	73	61.2 (6.2)	NR	NR	18.3	46.4	39.4	14	2.9	9.9
Trifecta															
Anselmi, 2017 [15]	France	2008–2014	RS	824	75 (7.7)	56	60.8	1.3	33.5	9.6	96	4	0	0.7	7
Bavaria, 2014 [16]	Multicentre	2007–2009	RS	1014	73 (9.0)	64	NR	8.1	49.3	29.1	54.8	6	39.2	NR	0
Biancari, 2020 [17]	Finland	2008–2017	RS	851	74 (6.4)	50	NR	1.2	12	24	100	0	0	0	5
Fukuhara, 2020 [18]	USA	2011–2015	RS	508	70 (11.4)	60	58.8	NR	NR	7.7	85	30.1	17.9	7.9	0
Goldman, 2017 [19]	USA, Canada	2007–2009	RS	710	72 (9.3)	66	NR	28.6	50.8	NR	51.6	6.3	42.1	NR	58
Kilic, 2019 [20]	USA	2011–2017	RS	1953	72 (10.8)	62	53.9	15	NR	13.7	NR	NR	NR	NR	55
Lehman, 2020 [21]	Germany	2007–2018	RS	1241	72 (8.0)	60	NR	NR	NR	9.6	NR	NR	NR	3.20	NR
Lam, 2020 [22]	Netherlands	2009–2018	RS	719	74 (6.4)	54	NR	NR	NR	NR	69.9	30.1	0	7.2	58
Raimundo, 2018 [23]	Portugal	2011–2016	RS	556	73 (9.0)	58	NR	NR	NR	11.2	68.9	9.5	15.8	4.5	54
Cerqueira, 2018 [24]	Portugal	2009–2016	PS	329	75	49	NR	4	34	6	73			5	NR
Freedom Solo															
Cerqueira, 2018 [24]	Portugal	2009–2016	PS	329	74	51	NR	4	36	8	73			5	NR
Fleerakkers, 2018 [25]	Belgium	2009–2017	RS	625	76	48.3	NR	10.6	13.6	0	79.5	6.4	11.4	2.4	NR
Repossini, 2016 [26]	Italy	2004–2009	RS	565	75	57.2	NR	1.6	41.7	4.2	91.4	6.3	2.3	4.2	38.05
Wollersheim, 2016 [27]	Netherlands	2005–2014	RS	350	76	48	NR	3	65		74	4	22	3	46.29
Freestyle															
Ennker, 2016 [28]	Germany	1996–2007	PS	2551	72	55	NR	9.6			90	62.9	52.3	NR	0
Amabile, 2014 [29]	France	1997–2004	PS	500	74.5	52	58.6	2	41	3	88	7	3	2	31.4
Kappetein, 2007 [30]	Netherlands	1992–2001	PS	725	72	55.4	NR	NR	NR	NR	NR	NR	NR	NT	NR
Mohammadi, 2014 [31]	Canada	1993–2013	PS	531	67.6	56.3	NR		71	29.7	81	8	11	1.1	32.77
Magna Ease															
Anselmi, 2019 [32]	France	2008–2015	RS	849	74.1 (9.1)	47.8	61.1	3	32.9	NR	94.7	5.3	NR	2.7	NR
Lam, 2019 [22]	Netherlands	2009–2018	RS	923	71.2 (7.8)	71.18	NR	8.56	NR	9.43				6.18	NR
Biancari, 2020 [17]	Finland	2008–2017	RS	1365	73.9 (6.9)	58.5	NR	1.8		23					NR
Sorin Mitroflow															
Anantha Narayanan, 2015 [33]	USA	2004–2011	RS	1003	74.8 (9.8)	60.7	58.4	5.1	63.6	16.7				1.5	NR
Yankah, 2008 [34]	Germany	1986–2007	RS	1513	73.2 (0.2)	29.2	NR	NR	55.7	0.86	46.7	18.4	32.2	16	NR
Minami, 2005 [35]	Germany	1985–2004	RS	1516	75.6	29.8	NR	NR	NR	NR	3.8	33.8	62.4		3.89
Piccardo, 2016 [36]	France	1994–2011	RS	728	76 (6)	57	62	5	44	NR	91	9	NR	2.5	6.73
Ross															
Sievers, 2016 [37]	Germany	1990–2013	RS	1779	44.7 (11.6)	75.3	NR	NR	NR	64.8	23.8	22.4	51.7	NR	48
Sharifulin, 2019 [38]	Russia	1998–2015	RS	793	46.5 (12.4)	75.9	62.2	4.82	68.4	38.6	46.9	41	12.1	18.5	24
Martin, 2017 [39]	Quebec, Canada	1990–2014	RS	310	40.8 (10.6)	60.3	62.5	15.2	51.6	73.2	72.6	19.4	7.4	3.9	29.03
Mastrobuoni, 2016 [40]	Belgium	1991–2014	RS	306	41.7 (9.7)	74.8	NR	9.2	29.5	58.5	68	31.3		8.2	17.65
Brown, 2011 [41]	USA	1994–2010	RS	230	42.4 (9.7)	62	NR	24	23	71	50	50	0	10	54.78
Miskovic, 2016 [42]	Germany	1996–2014	RS	209	43 (10)	76	NR	8.1	44.6	78.5	50.7	26.3	23	9.1	42.11
David, 2018 [43]	Toronto, Canada	1990–2004	RS	212	Median 34	66	NR	20.1	17	71.7	NR	NR	NR	0.9	70.75

[a]Autologous pericardium patients only.

AI: aortic insufficiency; AS: aortic stenosis; AVNeo: aortic valve neocuspidization; BAV: bicuspid aortic valve; IE: infective endocarditis; LVEF: left ventricular ejection fraction; NR: not reported; NYHA: New York Heart Association; PS: prospective; RS: retrospective; SD: standard deviation.

Table 4: Meta-analysis of event rates per patient-years of follow-up in the available studies

		SVD			Endocarditis			Reintervention		
		Event/patient-years	95% CI	*P*-value	Event/patient-years	95% CI	*P*-value	Event/patient-years	95% CI	*P*-value
Ozaki		0.0034	0.0006–0.0087		0.0045	0.0012–0.0101		0.0107	0.0037–0.0212	
	Magna-Ease	0.0003	0.0002–0.0025	0.09	0.0010	0.0003–0.022	0.06	0.0013	0.0008–0.0020	0.002
	Trifecta	0.0034	0.0021–0.0051	0.99	0.0038	0.0025–0.0055	0.77	0.0055	0.0038–0.0076	0.20
	Ross	0.0056	0.0029–0.0090	0.44	0.0023	0.0012–0.0038	0.29	0.0081	0.0060–0.0104	0.55
	Freedom Solo	0.0094	0.0023–0.0214	0.21	0.0050	0.0036–0.0066	0.85	0.0072	0.0055–0.0092	0.41
	Freestyle	0.0036	0.0012–0.0075	0.94	0.0031	0.0020–0.0045	0.53	0.0050	0.0011–0.0117	0.26
	Sorin Mitroflow	0.0098	0.0078–0.0120	0.03	0.0039	0.0020–0.0065	0.81	0.0102	0.0070–0.0140	0.92
Magna-Ease		0.0003	0.0002–0.0025		0.0010	0.0003–0.022		0.0013	0.0008–0.0020	
	Ozaki	0.0034	0.0006–0.0087	0.09	0.0045	0.0012–0.0101	0.06	0.0107	0.0037–0.0212	0.002
	Trifecta	0.0034	0.0021–0.0051	0.02	0.0038	0.0025–0.0055	0.003	0.0055	0.0038–0.0076	<0.0001
	Ross	0.0056	0.0029–0.0090	0.004	0.0023	0.0012–0.0038	0.12	0.0081	0.0060–0.0104	<0.0001
	Freedom Solo	0.0094	0.0023–0.0214	0.008	0.0050	0.0036–0.0066	<0.0001	0.0072	0.0055–0.0092	<0.0001
	Freestyle	0.0036	0.0012–0.0075	0.05	0.0031	0.0020–0.0045	0.01	0.0050	0.0011–0.0117	0.09
	Sorin Mitroflow	0.0098	0.0078–0.0120	<0.0001	0.0039	0.0020–0.0065	0.01	0.0102	0.0070–0.0140	<0.0001

CI: confidence interval; SVD: structural valve degeneration.

AVNeo preserves the natural aortic root expansion in systole with maximal effective orifice area and very low transvalvular gradients. Increased transvalvular gradients and patient–prosthesis mismatch [50, 51] are independent predictors of cardiac events and mortality [52] following AV surgery. This advantage is particularly relevant where traditional bioprostheses have shown suboptimal performance [53, 54]. In particular, AVNeo should also be considered as a valid option in those with small aortic annuli or increased body mass index [3, 51], and in presence of severe left ventricular dysfunction [55]. Complex aortic annulus enlargement [56] procedures used to implant bigger size xenograft can be avoided if AVNeo is used [55]. AVNeo should also be considered as alternative to xenografts in active young active patients who may benefit from very low transvalvular gradient and in patients who want to avoid long-term anticoagulation (including women of child-bearing age).

Despite potential advantages and excellent results reported by Ozaki *et al.* [2], in western countries AVNeo has been adopted mainly in children and adolescents [8, 9]. The present AVNeo experience is the first reported in UK adult population and is the 5th series reported in Europe. Slow adoption in adults can be partially attributed to concerns about reproducibility and safety and the lack of mid- to long-term comparisons with modern bioprosthetic substitutes. Like previously published series, we had no intraoperative conversions, no operative morbidity nor mortality related to early valve failure. We also found that AVNeo is on par with most modern biological AV substitutes in terms of valve-related events, except for Magna Ease that showed the best performance in the present analysis. It should be noted that AVNeo series tended to include younger patients when compared to Magna Ease series. As SVD occurs sooner and more frequently in xenografts implanted in younger patients, the superiority of Magna Ease over AVNeo should be reassessed in a matched population. Outcomes with AVNeo did not change after excluding the series by Ozaki et al.

Notably, we failed to show any superiority from autografts (i.e. Ross) over other biological valve substitutes. Although the Ross procedure is commonly considered the gold standard for AVR in children and young adults, its role in adults remains controversial. Its complexity is balanced by its advantages of excellent haemodynamics, potential for a permanent AVR and no need for anticoagulation [57]. However, concerns over development of pulmonary autograft insufficiency have limited its application in adults. In particular, the risk of failure after aortic autograft implantation has been reported to be higher in patients with AI and dilated aortic annulus [57]. In older patients, there may also be difficulty finding a pulmonary artery of sufficient quality and matched size. Finally, postoperative control of blood pressure in adults may be crucial in avoiding autografts' mechanical adaptation phenomena (elastic fibre fragmentation), which can progress to root dilatation [57].

Limitations

Meta-analytic comparisons between valves were based on non-randomized data with differences in the study populations and follow-up duration. Most AVNeo series consisted of comparatively younger patients with shorter follow-up and

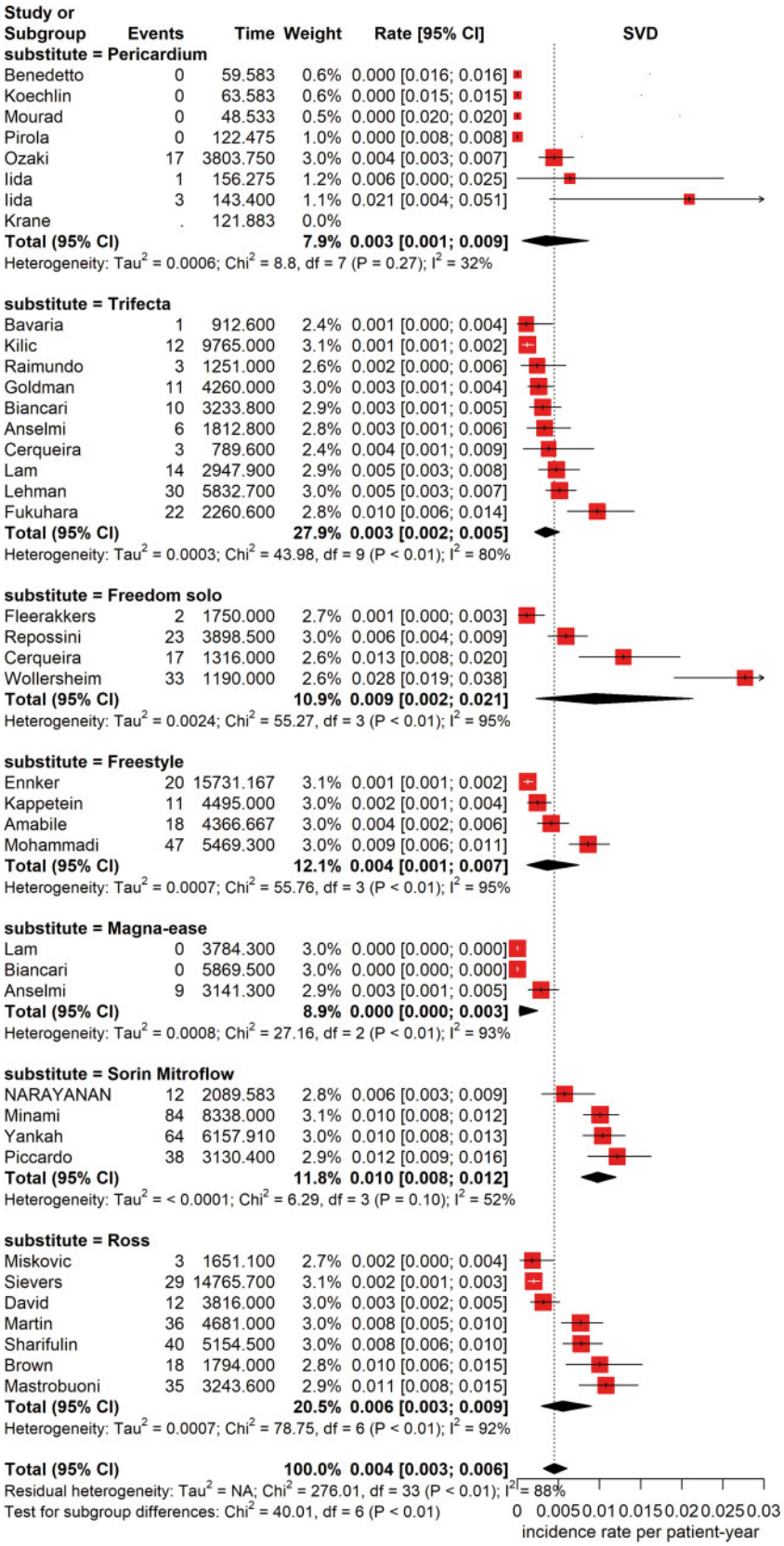

Figure 2: Forest plot of the incidence rate of SVD per patient-year. CI: confidence interval; SVD: structural valve degeneration.

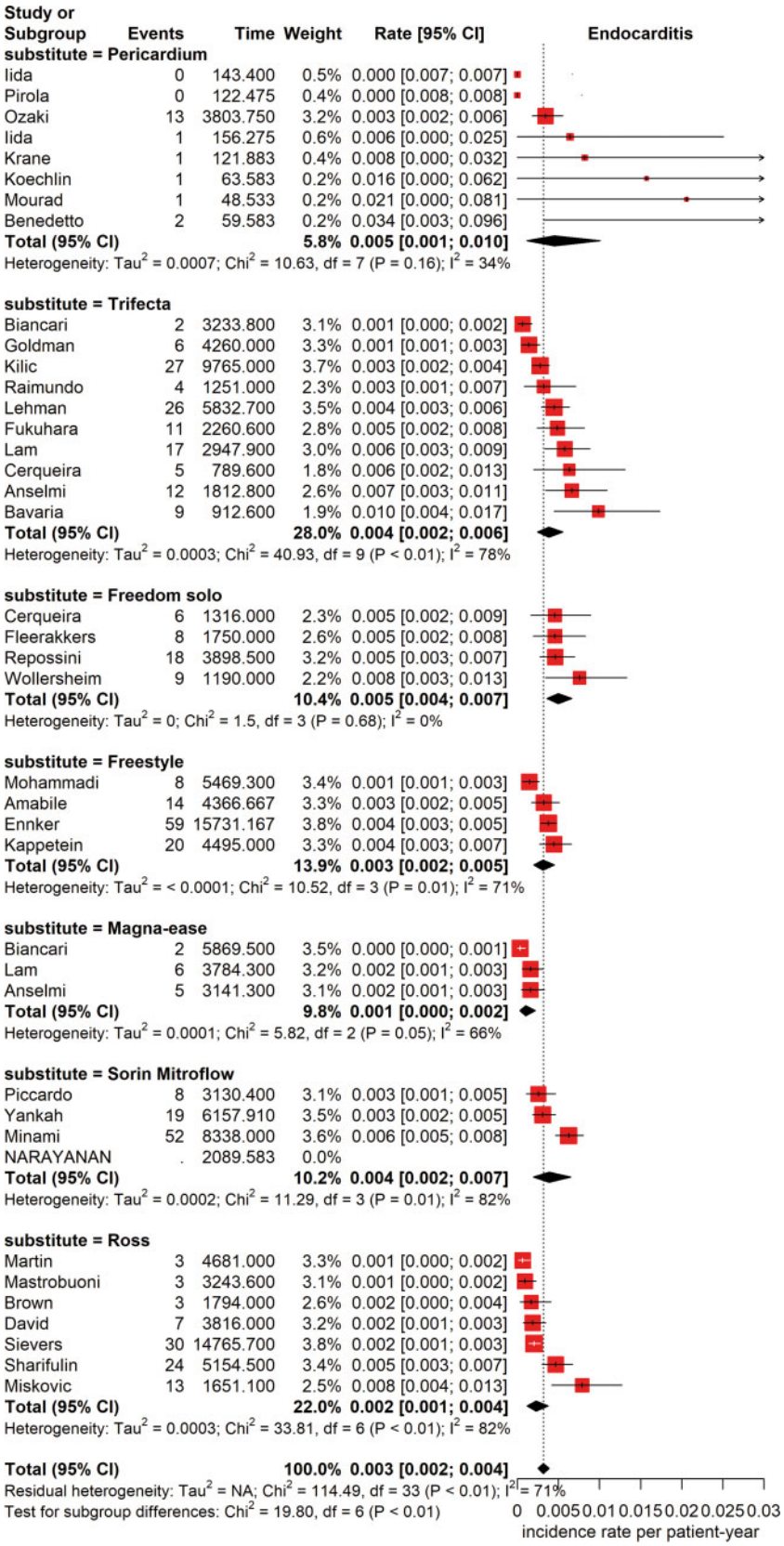

Figure 3: Forest plot incidence rate of endocarditis per patient-year. CI: confidence interval.

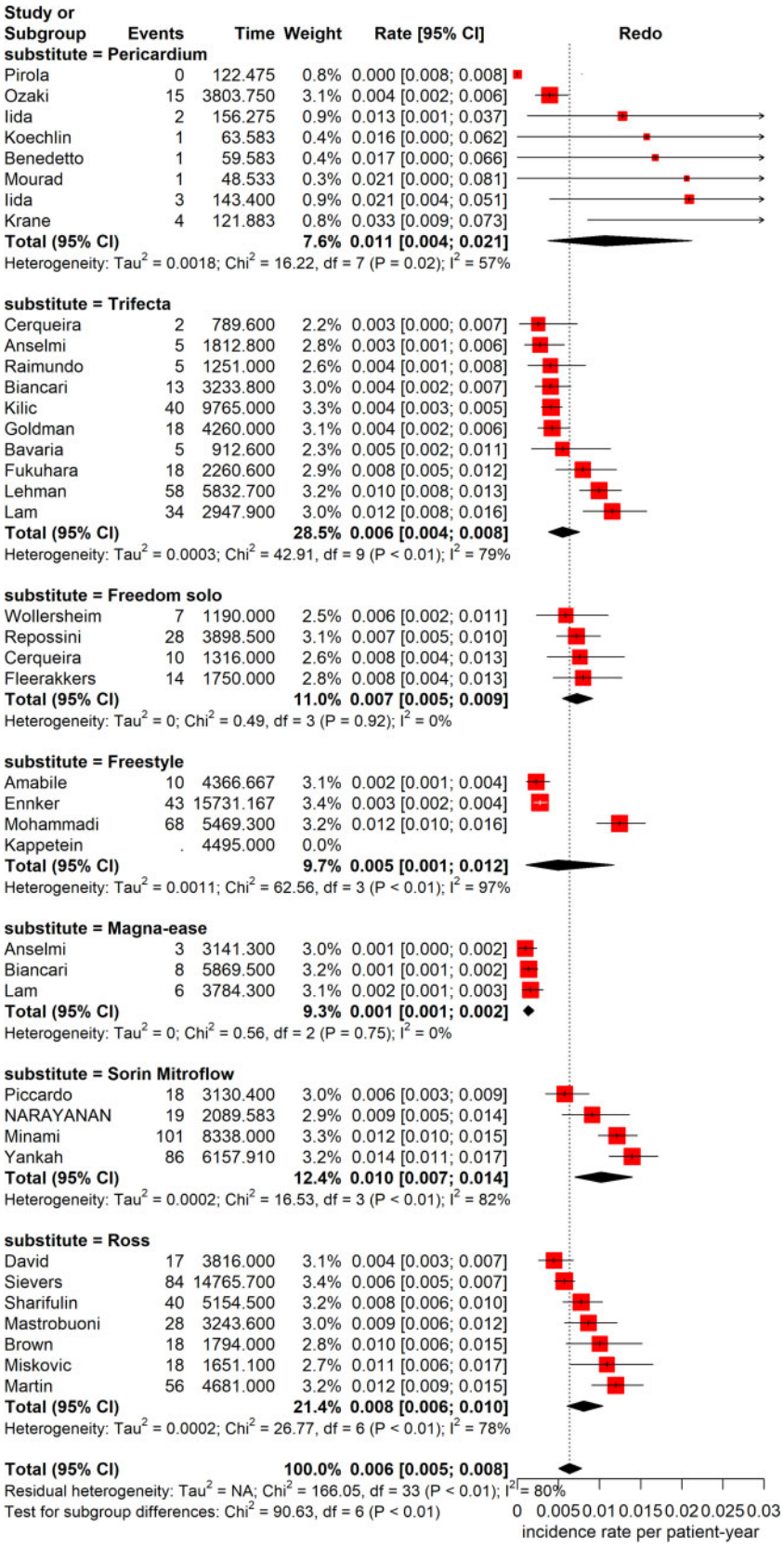

Figure 4: Forest plot incidence rate of reoperation per patient-year. CI: confidence interval.

limited single-centre experience. Hence, we focused only on valve-related outcomes (i.e. SVD) which are less influenced by patient risk profile, but confounding cannot be excluded. Results on postoperative transvalvular gradients were limited in the other populations and so we were unable to perform these comparisons.

Presently we did not include AVNeo procedures performed with alternative tissue substitutes such as tissue-engineered bovine pericardium. Results after AVNeo procedure are intrinsically related to the nature of the material used for leaflet reconstruction and the analysis of different substitutes must be kept separated. The majority of data on AVNeo in adult patients are associated with the use of autologous pericardium including the original series from Ozaki *et al.* [1]. Data on AVNeo using tissue-engineered bovine pericardium are scarce and initial reports have raised concerns on the use of this substitute during AVNeo procedure with almost 50% of failure at 3 years [58–60].

In the present series we excluded 2 patients from those that required reintervention for reason other than primary failure of the Ozaki valve. One patient who originally had combined Ozaki and mitral valve patch repair for aorto-mitral endocarditis, presented 3 months later with dehiscence of the mitral patch requiring re-repair. The Ozaki valve had only mild AI but had to be removed and replaced with a bioprosthesis to facilitate the exposure and revision of the mitral valve. The second patient was an active intravenous drug user who also had recurrence of endocarditis with a multi-microbial extensive root abscess and needed a hemi-Commando repair. We feel that this was related to her very high-risk lifestyle rather than the mechanics of the Ozaki valves. They have been included in the incidence of endocarditis.

CONCLUSION

In conclusion, the present analysis suggests that AVNeo is safe and is associated with mid-term risk of valve-related events that are comparable to most available biological valve substitutes. In view of excellent haemodynamic profile achieved with AVNeo [2, 13, 14, 61] and its beneficial implications in terms of functional recovery and survival [2, 3, 5], AVNeo can be considered as a possible solution particularly in active young patients who wish to avoid anticoagulation, those with small annuli and high body mass index. We found that Magna Ease was associated with a significantly lower risk of valve-related events compared to all other valves, including AVNeo. Therefore, Magna Ease is potentially the best biological choice as far as risk of reintervention is concerned. Future comparisons between AVNeo and other biological valve substitutes should ideally include evaluation of transvalvular gradients, incidence and degree of patient–prosthesis mismatch, index of left ventricular reverse remodelling and quality-of-life measures. Results from larger, multicentre studies are needed to assess the long-term outcomes following AVNeo.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

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Author contributions

Umberto Benedetto: Conceptualization; Data curation; Formal analysis; Methodology; Supervision; Writing—original draft; Writing—review & editing. **Shubhra Sinha:** Data curation; Methodology; Writing—original draft; Writing—review & editing. **Arnaldo Dimagli:** Conceptualization; Data curation; Formal analysis; Writing—original draft; Writing—review & editing. **Lauren Dixon:** Data curation; Writing—review & editing. **Serban Stoica:** Methodology; Writing—review & editing. **Lucia Cocomello:** Data curation; Methodology; Writing—original draft; Writing—review & editing. **Cesare Quarto:** Conceptualization; Writing—original draft; Writing—review & editing. **Gianni D. Angelini:** Conceptualization; Supervision; Writing—original draft; Writing—review & editing. **Uday Dandekar:** Conceptualization; Supervision; Writing—original draft; Writing—review & editing. **Massimo Caputo:** Conceptualization; Supervision; Writing—original draft; Writing—review & editing.

Reviewer information

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EDITORIAL COMMENT

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Do we need to rethink treatment of aortic valve pathologies in younger patients?

Markus Krane[a,b], Felix Wirth[a], Johannes Boehm[a], and Rüdiger Lange[a, b]

[a] Department of Cardiovascular Surgery, Division of Experimental Surgery, Institute Insure (Institute for Translational Cardiac Surgery), German Heart Center Munich, Munich, Germany
[b] DZHK (German Center for Cardiovascular Research) – Partner Site Munich Heart Alliance, Munich, Germany

* Corresponding author. German Heart Center Munich, Department for Cardiovascular Surgery, Lazarettstraße 36, 80636 Munich, Germany. Tel: +49-89-1218 4111; fax: +49-89-1218-4113; e-mail: Krane@dhm.mhn.de

Keywords: Aortic valve reconstruction • Aortic valve replacement • Ozaki procedure • Aotic valve pathology • Aortic Valve Neocuspidalization (AVNeo)

Currently, a wide range of treatment modalities exists for aortic valve pathologies. The options range from surgical and interventional replacement of the aortic valve with tissue (biological) devices, surgical replacement with mechanical devices and complex aortic valve repair strategies to preserve the native aortic valve in selected cases. While interventional and surgical valve replacement with biological devices is deemed to be the treatment of choice in elderly patients (>70 years), the preferred treatment modality in younger patients (<60 years) is still under discussion. For proper decision-making, the physician has to balance the specific risks of implantation, the long-term durability of the devices and the quality of life which may be affected by permanent anticoagulation or the need for pacemaker implantation. Hence, in younger patients below the age of 60 years, an "ideal" replacement device should meet the following criteria: low risk of implantation, extended long-term durability, optimal haemodynamics, low risk for permanent pacemaker implantation and no need for anticoagulation.

In 1995, Duran *et al.* (1) described the concept of de-novo aortic valve reconstruction using autologous pericardium. Chan *et al.* (2) reported a similar technique in 2011. In the same year, Ozaki *et al.* (3) described a standardized technique for this procedure (Ozaki procedure, Aortic Valve Neocuspidization—AVNeo). In addition, Ozaki developed corresponding leaflet sizers and cutting templates, which are commercially available and may facilitate the procedure, thus making it more reproducible.

Although early experience with AVNeo has shown promising results, long-term durability data are still lacking. In 2018, Ozaki *et al.* reported on their experience in a series of 850 patients undergoing AVNeo. The mean follow was 4.5 years with some patients reaching up to 10 years (4). The authors showed a cumulative incidence for reoperation of 4.2%. However, this and other studies suggested that the mode of degeneration between a commercially available tissue prosthesis and AVNeo using autologous pericardium may be substantially different. While the main indication for reoperation in biological prostheses seems to be a stenotic valve, the vast majority of re-operations after AVNeo was due to valve insufficiency or endocarditis.

During the last years, an increasing number of cardiac surgeons from the US, Europe, Africa and Asia has been learning the AVNeo procedure as an alternative option, especially for younger patients. The growing acceptance of the AVNeo procedure has led to more and more published results from different centers.

In the current issue of this journal, Benedetto *et al.* (5) report their results from two centers in the UK, together with a Meta-Analysis on more than 1200 AVNeo cases from different centers in Japan and across Europe. The UK experience comprises 55 patients undergoing AVNeo following the surgical technique described by Ozaki *et al.* The authors showed a freedom from the composite end-point (death, structural valve degeneration (SVD), reoperation and endocarditis) of 92.5% over a period of 24 months. Furthermore, they achieved low transvalvular gradients which are in accordance with other published data (6).