Early results from a prospective, single-arm European trial on decellularized allografts for aortic valve replacement: the ARISE study and ARISE Registry data

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Abstract: OBJECTIVES Decellularized aortic homografts (DAH) may provide an additional aortic valve replacement option for young patients due to their potential to overcome the high early failure rate of conventional allogenic and xenogenic aortic valve prostheses. METHODS A prospective, European Union-funded, single-arm, multicentre, safety study was conducted in 8 centres evaluating non-cryopreserved DAH for aortic valve replacement. RESULTS One hundred and forty-four patients (99 male) were prospectively enrolled between October 2015 and October 2018, mean age 33.6 ± 20.8 years; 45% had undergone previous cardiac operations. Mean implanted DAH diameter 22.6 ± 2.4 mm and mean durations for the operation, cardiopulmonary bypass and cross-clamp were 341 ± 140, 174 ± 80 and 126 ± 43 min, respectively. There were 2 early deaths (1 LCA thrombus on day 3 and 1 ventricular arrhythmia 5 h postop) and 1 late death due to endocarditis 4 months postoperatively, resulting in a total mortality of 2.08%. One pacemaker implantation was necessary and 1 DAH was successfully repaired after 6 weeks for early regurgitation following subcoronary implantation. All other DAH were implanted as a free-standing root. After a mean follow-up of 1.54 ± 0.81 years, the primary efficacy end points peak gradient (mean 11.8 ± 7.5 mmHg) and regurgitation (mean 0.42 ± 0.49, grade 0-3) were excellent. At 2.5 years, freedom from explantation/endocarditis/bleeding/stroke was 98.4 ± 1.1%/99.4 ± 0.6%/99.1 ± 0.9%/99.2 ± 0.8%, respectively, with results almost identical to those in an age-matched Ross operation cohort of 212 patients (mean age 34 years) despite DAH patients having undergone >2× more previous procedures. CONCLUSIONS The initial results of the prospective multicentre ARISE trial show DAH to be safe for aortic valve replacement with excellent haemodynamics in the short follow-up period.

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Early results from a prospective, single-arm European trial on decellularized allografts for aortic valve replacement: the ARISE study and ARISE Registry data

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Key question

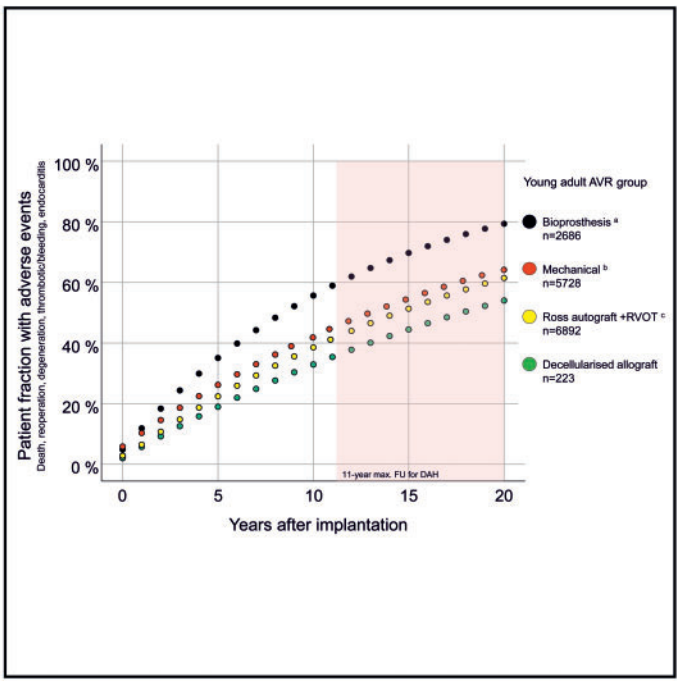
Are decellularized aortic homografts (DAH) a viable option for aortic valve replacement (AVR) in young patients?

Key finding(s)

144 patients, freedom from explantation/endocarditis/bleeding/stroke at 2.5 years: 98.4±1.1/99.4±0.6/99.1±0.9/99.2±0.8 %.

Take-home message

Initial results of the multicenter ARISE trial show DAH to be safe for AVR with excellent haemodynamics in the short follow-up period available.



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†The first two authors contributed equally to this study.

Abstract

OBJECTIVES: Decellularized aortic homografts (DAH) may provide an additional aortic valve replacement option for young patients due to their potential to overcome the high early failure rate of conventional allogenic and xenogenic aortic valve prostheses.

METHODS: A prospective, European Union-funded, single-arm, multicentre, safety study was conducted in 8 centres evaluating non-cryopreserved DAH for aortic valve replacement.

RESULTS: One hundred and forty-four patients (99 male) were prospectively enrolled between October 2015 and October 2018, mean age 33.6 ± 20.8 years; 45% had undergone previous cardiac operations. Mean implanted DAH diameter 22.6 ± 2.4 mm and mean durations for the operation, cardiopulmonary bypass and cross-clamp were 341 ± 140, 174 ± 80 and 126 ± 43 min, respectively. There were 2 early deaths (1 LCA thrombus on day 3 and 1 ventricular arrhythmia 5 h postop) and 1 late death due to endocarditis 4 months postoperatively, resulting in a total mortality of 2.08%. One pacemaker implantation was necessary and 1 DAH was successfully repaired after 6 weeks for early regurgitation following subcoronary implantation. All other DAH were implanted as a free-standing root. After a mean follow-up of 1.54 ± 0.81 years, the primary efficacy end points peak gradient (mean 11.8 ± 7.5 mmHg) and regurgitation (mean 0.42 ± 0.49, grade 0–3) were excellent. At 2.5 years, freedom from explantation/endocarditis/bleeding/stroke was 98.4 ± 1.1%/99.4 ± 0.6%/99.1 ± 0.9%/99.2 ± 0.8%, respectively, with results almost identical to those in an age-matched Ross operation cohort of 212 patients (mean age 34 years) despite DAH patients having undergone >2× more previous procedures.

CONCLUSIONS: The initial results of the prospective multicentre ARISE trial show DAH to be safe for aortic valve replacement with excellent haemodynamics in the short follow-up period.

Keywords: Aortic valve disease • Tissue engineering • Decellularization • Allografts

ABBREVIATIONS

AVR	Aortic valve replacement
CPB	Cardiopulmonary bypass
DAH	Decellularized aortic homograft

INTRODUCTION

Aortic valve replacement (AVR) in young adult patients still presents a major challenge with a difficult choice between multiple suboptimal surgical options for patients once valve repair is not feasible.

Conventional xenogenic biological heart valve prostheses have shown limited durability, especially in very young patients. In some cases, rapid deterioration of valve function has even resulted in sudden cardiac death [1]. However, the option of industrially manufactured biological valves is nevertheless preferable for some patients, despite the associated higher reoperation rates, as it does not require lifelong anticoagulation medication [2, 3].

Mechanical valves provide excellent long-term durability and are the method of choice for AVR in patients under 50 years of age in many centres worldwide [3, 4]. However, active patients and women wishing to start a family more frequently struggle with the inherent restrictions associated with in the strict, lifelong anticoagulation regime required to avoid mechanical valve thrombosis. In addition, there is a 1–1.5% risk of a severe bleeding or thrombotic event per patient-year [4]. The next generation of anticoagulants will hopefully help to reduce this risk in young patients, which appears considerable, given today's life expectancy. Until then, this risk can be minimized through patient education and anticoagulation self-management strategies [5].

The Ross autograft operation is considered the gold-standard for AVR in young patients [6]. However, despite the excellent long-term results reported for the procedure, it has not been adapted by the vast majority of cardiac surgeons due to its technical complexity and a reluctance to create a potential 2-valve problem for the patient in the future. In addition, a significant number of patients undergoing AVR are not good candidates for a Ross procedure, a fact sometimes neglected by advocates of the approach. Patients with bicuspid aortic valves, rheumatic or connective tissue disease and patients with associated dilatation of the ascending aorta are not ideal Ross candidates. The same applies for patients with comorbid mitral disease or multiple previous AVR due to congenital heart defects.

Cryopreserved human aortic valves are currently rarely used for planned AVR, as durability in young patients is limited due to pronounced calcification, leading to increased morbidity during redo operations. In extensive aortic root endocarditis, allograft AVR remains the procedure of choice due to the unique ability to restore normal anatomy [7, 8].

Decellularized allografts have been in clinical use for more than a decade and may provide an additional AVR option for young patients, as they can potentially overcome the high early failure rate of conventional allogenic and xenogeneic AVR prostheses due to reduced immunogenicity [9, 10]. There have been conflicting reports on the results of various processing methods used for decellularization, which have led to calls for prospective long-term studies on decellularized allografts for AVR [11–13].

The aim of this study therefore is to (i) present early data from the first prospective, European-wide trial on decellularized aortic homograft (DAH) for AVR and (ii) to compare current DAH results from the ARISE Registry with contemporary data on the Ross procedure and other AVR options for young adults.

MATERIALS AND METHODS

Study setting

The ARISE study received funding from the European Union's HORIZON 2020 Programme under grant agreement no. 643597. The funding covered homograft procurement, homograft processing and data collection. Corlife oHG provided the decellularization service for the homografts and sponsored the study according to good clinical practice requirements.

The study was registered under ClinicalTrials.gov, NCT02 527629, and received the European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP®) seal as a Post Authorization Safety Study, EU PAS 10201. The study was also registered with the German Federal Institute for Vaccines and Biomedicines (www.pei.de) under Ref. Number NIS322.

Approval was given by all local ethics committees prior to the start of the study, and informed consent was obtained appropriately from all participants or parents (MHH no. 2840-2015). Indication for AVR according to the 2017 European Society of Cardiology/ European Association for Cardio-Thoracic Surgery guidelines for valvular heart disease was the key inclusion criterion without age limits; patients with active endocarditis were excluded.

Patients were not included consecutively and patient selection was based on the decision of the respective centre, availability of an appropriate homograft and patient consent. Surgical procedures were performed according to locally established standard procedures under cardiopulmonary bypass (CPB). Postoperative anticoagulation with Warfarin was recommended for 2 months, followed by ASA at 100 mg per day to be continued as a permanent medication regime.

The calculated sample size was 120 patients based on the average of 5.4% adverse clinical events per patient-year reported for mechanical valves and biological valves during follow-up, including sustained structural valve deterioration, non-structural valve dysfunction, thromboembolism and bleeding, and endocarditis [8].

The primary end points were periprocedural complications (all-cause mortality, major stroke, life-threatening or disabling bleeding, acute kidney injury requiring renal replacement therapy, myocardial infarction, major vascular complications) and heart valve dysfunction (aortic valve area $\leq$ 1.2 cm^2 and mean aortic valve gradient $\geq$ 20 mmHg or peak velocity $\geq$ 3 m/s, or moderate or severe prosthetic valve aortic regurgitation) and repeat procedure for valve-related dysfunction (surgical or interventional therapy).

Homograft procurement and processing

Homografts were procured in line with the current European Directive 2004/23, as amended, via 4 different tissue banks (European Homograft Bank, Brussels, Dr R. Jashari; German Society for Tissue Transplantation—DGFG, Hannover, M. Börgel; EuroTissue Bank, Rotterdam, A. van den Bogaerdt; Banc de Sang i Teixits, Barcelona, Dr E. Trias) and shipped to Hannover for processing at corlife oHG (www.corlife.eu).

DAH was authorized by the German competent authority as the medicinal product 'Cell-free aortic heart valve, Arise AV', # PEI.G.11766.01.1. The processing of each homograft comprises ~30 different steps using a detergent-based, non-cryopreservation approach as described previously [14]. Microbiological assessment was performed as part of the incoming inspection, both during and after processing with a final 14-day quarantine. Each homograft was assessed histologically following processing, and the residual dsDNA content was measured after processing and prior to final release. Reference samples of all homografts were stored in accordance with German law for at least 1 year.

Statistical analysis

Summaries of numeric data are given as means and standard deviation. The proportion of explanted and dysfunctional grafts over time was calculated and a peak echocardiographic gradient of $\geq$ 50 mmHg and regurgitation $\geq$ moderate was defined as dysfunctional.

Time-related events, such as freedom from explantation and degeneration, were evaluated according to Kaplan–Meier.

We calculated perioperative and annual adverse events such as death, reoperation or reintervention, valve degeneration, thrombotic and bleeding events and endocarditis for all DAH implanted to date from the ARISE Registry, which has a 100% follow-up of all patients having received a DAH to date, and compared them with the results of recent large-scale meta-analyses for bioprostheses, mechanical valves and the Ross procedure in young adults, provided by the group of Johanna Takkenberg. We also included the actually observed freedom from any adverse event curve for DAH ±95% confidence intervals to this comparison to allow for direct comparison [4, 15, 16].

The long-term extrapolation was performed by simply adding the observed early and annual rates for adverse incidents. Annual event rates were calculated based on the respective event-free patient fraction to date.

We did not test for statistical significance due to the significant differences in data sets, i.e. prospectively collected data from a controlled multicentre trial and meta-analyses summarizing almost entirely retrospective and single-centre studies and the limited follow-up of the DAH cohort.

SPSS 25 (IBM Corporation, Somer, NY, USA) was used for the analyses.

RESULTS

Perioperative outcome

One hundred and forty-four patients (99 male) were prospectively enrolled in the ARISE Trial between October 2015 and October 2018 with a mean age of 33.6 ± 20.8 years. Twenty-eight percent were paediatric patients and 45% of the patients had undergone previous cardiac operations. Nineteen percent underwent 2 or more previous surgical procedures. The mean implanted DAH diameter was 22.6 ± 2.4 mm. The mean operation duration was 341 ± 1.40 min, the mean CPB time was 174 ± 80 min and the mean cross-clamp time 126 ± 43 min. No postoperative bypass grafting or renal replacement therapy was required.

Figure 1 shows the patient numbers per site within the ARISE study. Table 1 gives an overview of the characteristics of the ARISE study cohort and the ARISE Registry cohort of all DAH implanted to date. This registry includes the ARISE study patients and all patients having received DAH prior to and outside the clinical study, e.g. in centres, which did not participate in the ARISE study.

There were 2 early deaths in the cohort: 1 patient suffered cardiac arrest due to an LCA thrombus on postoperative day 3 while on the normal ward and subsequently died, despite extracorporeal assist due to multi-organ failure. The most likely explanation was an embolus from the left atrium associated with a simultaneous mitral valve procedure during DAH implantation, as emergency coronary angiography showed no stenosis at ostial level or any kinking of the main stem.

The other patient died due to sustained ventricular arrhythmia 5 h postoperatively despite extracorporeal assist for a suspected coronary reimplantation problem following explantation of a heavily calcified cryopreserved homograft. However, the autopsy

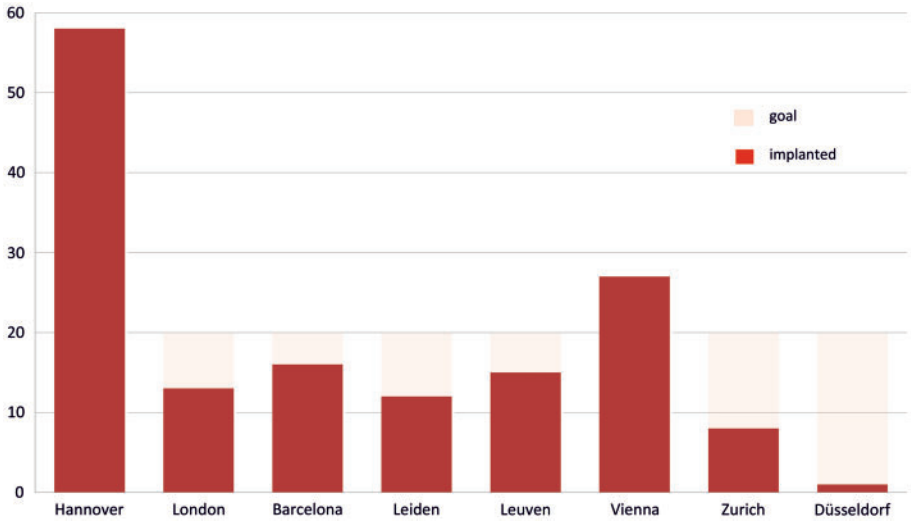

Figure 1: Patient inclusion within the prospective multicentre ARISE trial by centre.

Table 1: Patient characteristics for the ARISE study and the ARISE Registry cohort including all DAH implanted to date

	ARISE study cohort (*N* = 144)	All DAH (*N* = 223)
Implantation period	2015–2018	2008–2019
Age at implantation (years), mean (SD)	33.6 (20.8)	28.7 (19.8)
Follow-up (years), mean (SD)	1.54 (0.81)	2.60 (2.13)
Total follow-up (years), *n*	222	581
Male gender, *n* (%)	99 (69)	151 (68)
Number of previous operations, *n*		
0	79	119
1	38	64
2	19	25
>2	8	15
Type of previous procedures, *n*		
1 × aortic valve replacement	19	30
2 × aortic valve replacement	5	8
Catheter-based intervention	23	48
Aortic valve repair	6	23
Allograft diameter (mm), mean (SD)	22.6 (2.4)	22.6 (2.9)
10–18	9	18
19–22	56	82
23–29	79	123
Implantation time (min), mean (SD)		
Total operation	341 (140)	348 (131)
Cardiopulmonary bypass	174 (80)	190 (88)
Cross-clamp	126 (43)	132 (46)
Latest echocardiography		
Aortic annulus (mm), mean (SD)	23.7 (2.5)	21.9 (4.0)
Aortic annulus, *z*-score, mean (SD)	0.53 (1.6)	0.20 (1.51)
Effective orifice area (cm^2), mean (SD)	3.1 (0.9)	2.9 (0.8)
Peak gradient (mmHg), mean (SD)	11.8 (7.5)	14.8 (15.1)
Regurgitation, grade 0–3, mean (SD)	0.42 (0.49)	0.53 (0.57)
LV ejection fraction (%), mean (SD)	64.2 (4.3)	62.7 (8.4)

DAH: decellularized aortic homograft; SD: standard deviation.

showed patent coronary arteries and normal suture lines as well as severe left ventricular hypertrophy and an old myocardial infarction, which occurred during implantation of the cryopreserved homograft 18 years ago. In addition, 1 further patient died 4 months postoperatively during introduction of anaesthesia for reoperation due to endocarditis-associated complications, resulting in a total mortality of 2.08%.

One pacemaker implantation was necessary for atrioventricular block and 1 DAH was successfully repaired for early regurgitation after 6 weeks. No signs of endocarditis were observed during redo, and technical problems in the initial operation were identified.

This was also the only DAH implanted in subcoronary position; all other DAHs were implanted as free-standing root replacements without significant reinforcement procedures.

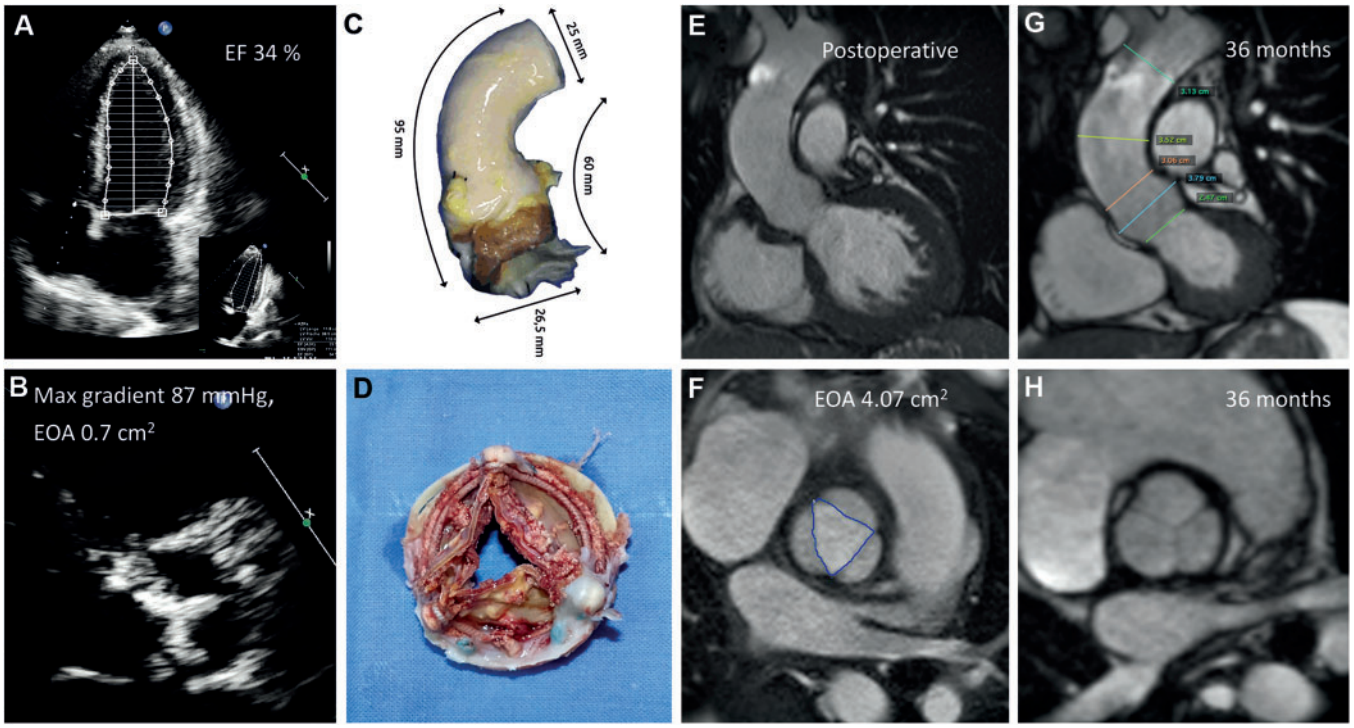

Figure 2: Twenty four-year-old male patient, 1/2009 aortic valve replacement with 25 mm Carpentier Edwards Perimount valve (will of patient) and supracommissural replacement of the ascending aorta using a 24-mm Hemashield vascular prosthesis. (**A**, **B**) Severe calcified aortic stenosis and impaired left ventricular function with pleural effusion. (**C**, **D**) Extended aortic valve replacement including the Hemashield prosthesis using a long decellularized homograft provided by the European Homograft Bank and explanted bioprosthesis. (**E**, **F**) CMR at discharge. (**G**, **H**) Postoperatively LV function recovery due to a large effective orifice area and normal valve function in the 36 months follow-up so far. No signs of ascending aorta dilatation. EF: ejection fraction; EOA: effective orifice area.

Initial follow-up results within the prospective ARISE study cohort

After a mean follow-up of 1.54 ± 0.81 years, the primary efficacy end points of mean peak gradient (11.8 ± 7.5 mmHg) and regurgitation (mean 0.42 ± 0.49, grade 0–3) were excellent.

Freedom from explantation, endocarditis, bleeding and stroke at 2.5 years was 98.4 ± 1.1%, 99.4 ± 0.6%, 99.1 ± 0.9% and 99.2 ± 0.8%, respectively. These results were almost identical to those from the age-matched Ross cohort of 212 patients (mean age 34 years) despite a higher number (>2×) of previous procedures in DAH patients [17]. Figure 2 gives an example by demonstrating the preoperative situation and postoperative course of the first patient included in the ARISE study.

Figure 3 shows freedom from death and freedom from homograft explantation for the 144 ARISE Trial patients. Figure 4 shows freedom from stenosis and regurgitation, and Fig. 5 displays freedom from any reintervention and freedom from endocarditis.

Comparison with published Ross-autograft procedure cohorts

Table 2 lists freedom from diverse adverse outcomes within the ARISE study ($n = 144$) and the ARISE Registry ($n = 223$) compared with the Ross cohort published by David *et al.* [17] ($n = 212$) and a large recent Ross review provided by Takkenberg *et al.* [16] summarizing published results from 6892 adult patients. The DAH results were comparable to the Ross results for freedom from death, endocarditis, major bleeding and thrombotic events at 5 years follow-up. Freedom from reoperation and freedom from valve degeneration was lower in DAH patients, who were younger (28.7 ± 19.8 vs 41.9 ± 11.4 years) with paediatric patients comprising 38% of the ARISE Registry cohort.

Expected adverse events for contemporary aortic valve replacement options for young adults

Perioperative and annual adverse events such as death, reoperation or reintervention, valve degeneration, thrombotic and bleeding events and endocarditis were calculated for conventional aortic bioprostheses, mechanical valves, the Ross procedure and DAH to provide an overview of expected adverse events per patient. Data were taken from recent large-scale meta-analyses from Takkenberg *et al.* [4, 15, 16].

Figure 6 shows DAH in young adults with comparable performance to the conventional alternatives of mechanical valves, the Ross procedure and standard bioprostheses.

DISCUSSION

Surgeons counselling young patients referred for AVR are regularly confronted with the limitations of today's surgical arsenal. As a consequence, decision-making tends to be influenced by the patient's lifestyle and feared restrictions to quality of life. This has led to an increasing trend towards bioprosthetic aortic valves for younger patients despite higher reoperation rates, in part

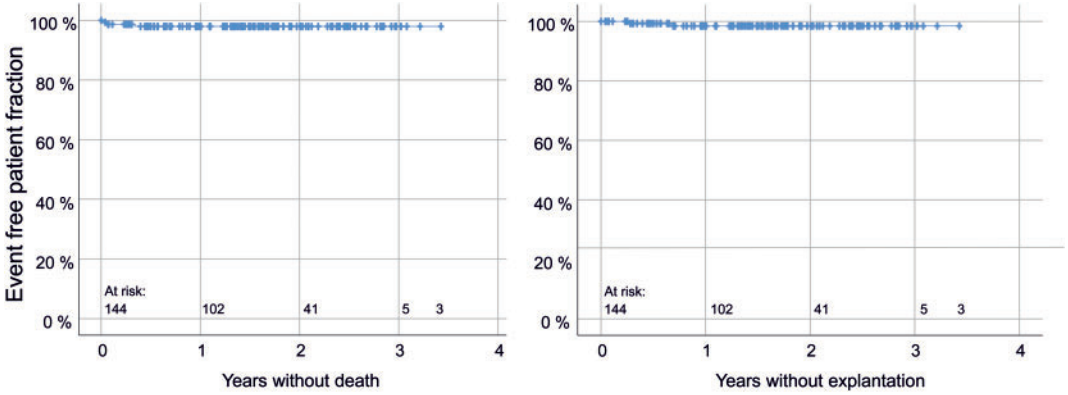

Figure 3: Freedom from death and freedom from allograft explantation for the ARISE study patients.

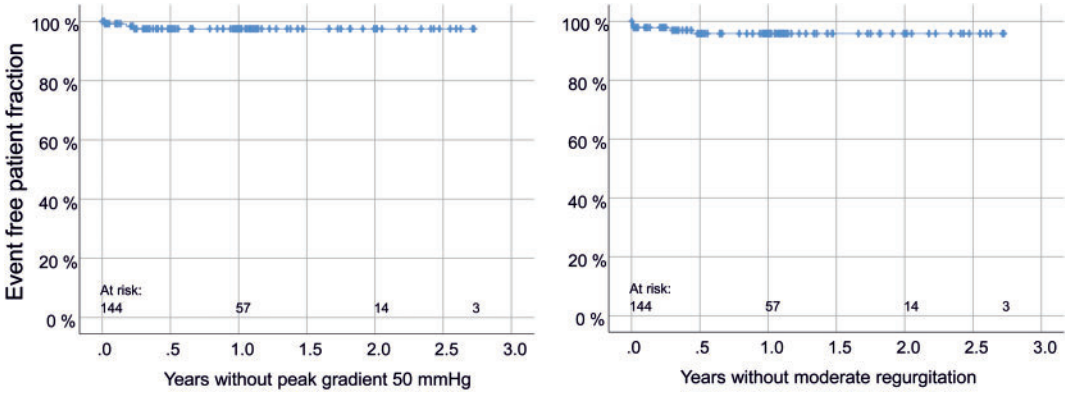

Figure 4: Freedom from aortic valve stenosis and regurgitation for the ARISE study patients.

driven by the low incidence of mortality (in some cases 2.5%) reported for redo AVR [3, 18]. However, this can be misleading, as the population-based 30-day mortality rate for redo AVR has been demonstrated to be as high as 4.8% in patients aged 18–55 [2, 3].

In general, the Ross operation is a good option for a young adult patient as reoperation rates in the first 2 decades are low [19]. However, it is highly likely that repeated 2-valve surgery will be necessary within the lifetime of these patients and future research will have to assess whether this negatively impacts long-term survival after 3 or more decades [16].

Intra-annular procedures are preferred by many surgeons and centres to reduce operative complexity, due to concerns regarding an increased risk for perioperative mortality in aortic root procedures. However, recent data from large-scale meta-analyses focusing only on AVR in young adults suggest that early mortality for the Ross operation is even lower than for bioprosthetic or mechanical AVR [4, 15, 16]. In addition, the 10-year mortality rates for bioprosthetic and mechanical AVR were poorer than those for the Ross operation [3, 17].

Nevertheless, a large group of patients, including patients with congenital heart defects or multiple previous surgical procedures, are not good candidates for the Ross procedure, limiting its application.

The current study adds important information on alternatives for AVR, as the ARISE study is the first prospectively conducted multicentre trial on DAHs as an additional biological option for AVR in young patients. The results show excellent early haemodynamic results and no specific problems in terms of perioperative handling issues. The early mortality rates were almost identical to those reported for Ross patients [16, 17, 20, 21], which is excellent given the 2 times higher rates of previous aortic valve procedures in the DAH cohort. Coronary reimplantation in DAH was uncomplicated with no need for intraoperative bypass grafting. In the Ross procedure, the rate for intraoperative coronary artery bypass grafting has been reported as 5% in young adults and 6.5% in children [16]. Given the widespread expertise in aortic root remodelling techniques such as the David procedure, we do not consider reimplantation of regular coronary arteries to be a factor likely to influence the outcome of the DAH cohort. Long-term patency has been shown for reimplanted coronary arteries in aortic root remodelling techniques and excellent results have been achieved for redo aortic root surgery [22]. Data from the ARISE Registry covering all implanted DAH to date with follow-up data of up to 11 years showed current DAH results to be well comparable with the contemporary results achieved with the Ross procedure (Fig. 6).

Decellularized aortic allografts have shown less HLA-response in humans and less calcification in animal models and in humans [23–25]. We have shown the absence of calcium in a DAH reoperation 4.5 years after implantation in an infant [9] and extensive *in vivo* recellularization with non-immunogenic recipient cells in

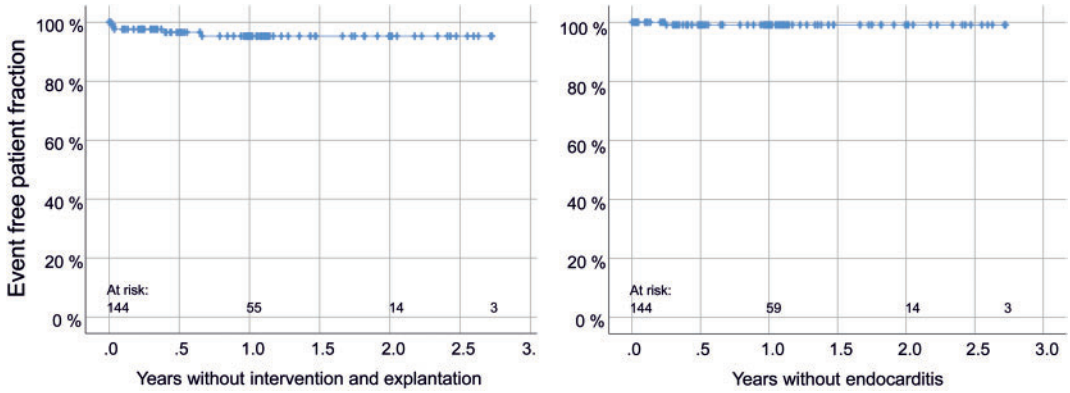

Figure 5: Freedom from any reintervention and endocarditis for the ARISE study patients.

Table 2: Freedom from diverse adverse outcomes for DAHs within the ARISE study and the ARISE Registry compared with the Ross cohort published by David *et al.* [17] and a large recent Ross review published by Takkenberg *et al.* [16]

Freedom from (%)	Cohort	At 2.5 years (%), mean ± SD	At 5 years (%), mean ± SD
Death	ARISE$_{(n = 144)}$	98.0 ± 1.2	NA
	All DAH$_{(n = 223)}$	98.2 ± 0.9	98.2 ± 0.9
	Ross$_{(n = 212)}$ [17]	NA	98.6
	Ross$_{(n=6892)}$ [16]	NA	97.0
Endocarditis	ARISE	99.4 ± 0.6	NA
	All DAH	99.1 ± 0.9	97.3 ± 2.2
	Ross [17]	NA	100
	Ross [16]	NA	98.4
Aortic valve reoperation (explantation or repair)	ARISE	98.4 ± 1.1	NA
	All DAH	97.5 ± 1.3	90.8 ± 4.0
	Ross [17]	NA	NA
	Ross [16]	NA	96.7
Aortic stenosis (>50 mmHg peak)	ARISE	97.5 ± 1.4	NA
	All DAH	94.0 ± 2.4	92.4 ± 2.8
	Ross [17]	NA	NA
	Ross [16]	NA	NA
Aortic regurgitation (≥moderate)	ARISE	95.8 ± 1.9	NA
	All DAH	96.0 ± 1.8	91.1 ± 3.8
	Ross [17]	NA	95.2
	Ross [16]	NA	NA
Aortic valve degeneration (stenosis and regurgitation)	ARISE	93.3 ± 2.3	NA
	All DAH	90.2 ± 2.8	85.3 ± 4.3
	Ross [17]	NA	NA
	Ross [16]	NA	95.9
Major bleeding	ARISE	99.1 ± 0.9	NA
	All DAH	99.5 ± 0.5	99.5 ± 0.5
	Ross [17]	NA	100
	Ross [16]	NA	99.5
Thrombotic event/stroke	ARISE	99.2 ± 0.8	NA
	All DAH	99.5 ± 0.5	99.5 ± 0.5
	Ross [17]	NA	100
	Ross [16]	NA	99

DAH: decellularized aortic homograft; NA: not applicable; SD: standard deviation.

decellularized pulmonary and aortic allografts [26]. Decellularized pulmonary homografts showed significantly higher freedom from reoperation at 10 years compared with cryopreserved pulmonary homografts and almost no early cellular immune response [10, 27]. The promising initial clinical results for DAH [9] led to the initiation of prospective multicentre trial, whose early results are reported here.

Given their restricted availability, which patients stand to benefit most from the implantation of a DAH? Clearly, patients who underwent multiple previous aortic root procedures during childhood or young patients after destructive endocarditis and patients with contraindications for the Ross operation or anticoagulation come into question here. Young adult female patients who would like to have children and in whom previous bioprostheses have failed are also good candidates, as permanent anticoagulation is not required. In addition, young patients with reduced LV function also are potential recipients for DAH, as homografts provide excellent effective orifice areas compared with intra-annular devices. Endocarditis, to our understanding, is not an indication for DAH, as the open matrix of a decellularized

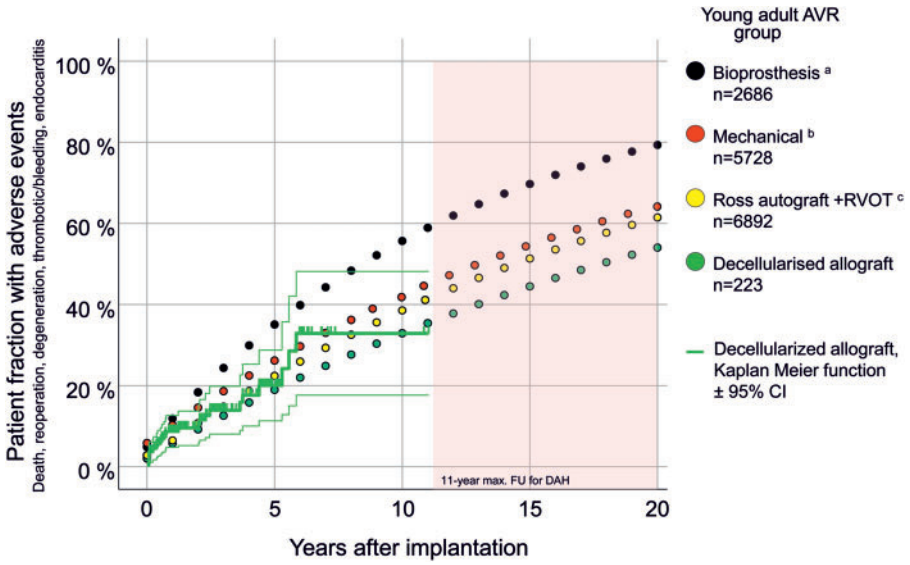

Figure 6: ARISE Registry data of all 223 decellularized aortic homograft (DAH) implanted to date compared with recently published meta-analysis data from several AVR options in young adult patients. Perioperative and annual adverse events such as death, reoperation or reintervention, valve degeneration, thrombotic and bleeding events and endocarditis were summarized to provide an estimate of adverse events in the long term. Additionally, actually observed adverse DAH events are shown in Kaplan–Meier function equivalent ±95% CI. Data taken from Refs [4, 15, 16]. AVR: aortic valve replacement; CI: confidence interval.

allograft may be more prone for bacterial invasion. Moreover, recellularization with patient's non-immune competent cells is the aim, which may be reduced in the setting of an active bacterial infection. Therefore, we consider active endocarditis as a contraindication for DAH.

The limited availability of adequately sized allografts is a drawback for DAH and availability is likely to be increasingly challenging if the long-term results correspond with the excellent short-to-medium results achieved to date and may also have an impact on the availability of conventional allografts for the treatment of aortic root endocarditis. Further research into xenogeneic alternatives using genetically modified animals is therefore needed. The current price for a decellularized homograft, either aortic or pulmonary, is roughly 20.000 €, which is divided in 4500–5000 € for the allograft procurement by the providing tissue bank, which also is allocating the homograft to a certain hospital. Fees for decellularization are currently ∼15 000 € and expected to come down as with any new technology over time development costs have been reimbursed. The price of the Melody transcatheter pulmonary valve at market introduction was in the same range and decreased by ∼30% over the years. One study on tissue-engineered pulmonary valves showed the potential to be cost-effective [28].

Limitations

The short overall follow-up available for DAH patients so far is the biggest limitation for the study, and definitive conclusions will require a longer follow-up period. Moreover, there are several limitations to the present study, including the one-armed study design and the restrictions inherent in the comparison of prospectively collected data from a controlled trial with retrospectively conducted single-centre analyses and meta-analyses based on such reports.

In addition, the transferability of direct conclusions from this study to other proprietary decellularization protocols is limited due to the variable influence of the individual protocols on cell removal, matrix preservation and subsequently allograft immunogenicity. Cost aspects have not been addressed within this analysis, as long-term efficacy for DAH is not available yet.

CONCLUSION

The initial results of the prospective multicentre ARISE trial demonstrate DAH to be safe for AVR with excellent haemodynamics in the short follow-up period available thus far. Early DAH results compare well with the early outcomes of contemporary Ross operation cohorts despite 2 times more previous cardiac procedures in DAH patients. The planned follow-up period of at least 10-(20) years will help to determine the suitability of DAH as a robust, long-term biological AVR option for young patients.

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Conflict of interest: Axel Haverich holds shares in corlife oHG, the company providing the service of processing decellularized allografts used in this study. Igor Tudorache is a medical consultant for corlife oHG and is involved in approval of homografts. Ramadan Jashari is a director of the European Homograft Bank. All other authors declared no conflict of interest.

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REFERENCES

[1] Saleeb SF, Gauvreau K, Mayer JE, Newburger JW. Aortic valve replacement with bovine pericardial tissue valve in children and young adults. Circulation 2019;139:983–5.

[2] Chiu P, Goldstone AB, Fischbein MP, Woo YJ. Current evidence for prosthesis selection: what can we really say? J Thorac Cardiovasc Surg 2019;158:368–75.

[3] Schnittman SR, Adams DH, Itagaki S, Toyoda N, Egorova NN, Chikwe J. Bioprosthetic aortic valve replacement: revisiting prosthesis choice in patients younger than 50 years old. J Thorac Cardiovasc Surg 2018;155:539–47.e9.

[4] Korteland NM, Etnel JRG, Arabkhani B, Mokhles MM, Mohamad A, Roos-Hesselink JW *et al*. Mechanical aortic valve replacement in nonelderly adults: meta-analysis and microsimulation. Eur Heart J 2017;38:3370–7.

[5] An KR, Belley-Cote EP, Um KJ, Gupta S, McClure GR, Jaffer IH *et al*. Antiplatelet therapy versus anticoagulation after surgical bioprosthetic aortic valve replacement: a systematic review and meta-analysis. Thromb Haemost 2019;119:328–39.

[6] Misfeld M, Borger MA. The Ross procedure: time to reevaluate the guidelines. J Thorac Cardiovasc Surg 2019;157:211–12.

[7] Preventza O, Mohamed AS, Cooley DA, Rodriguez V, Bakaeen FG, Cornwell LD *et al*. Homograft use in reoperative aortic root and proximal aortic surgery for endocarditis: a 12-year experience in high-risk patients. J Thorac Cardiovasc Surg 2014;148:989–94.

[8] Svensson LG, Adams DH, Bonow RO, Kouchoukos NT, Miller DC, O'Gara PT *et al*. Aortic valve and ascending aorta guidelines for management and quality measures: executive summary. Ann Thorac Surg 2013;95:1491–505.

[9] Tudorache I, Horke A, Cebotari S, Sarikouch S, Boethig D, Breymann T *et al*. Decellularized aortic homografts for aortic valve and aorta ascendens replacement. Eur J Cardiothorac Surg 2016;50:89–97.

[10] Neumann A, Sarikouch S, Breymann T, Cebotari S, Boethig D, Horke A *et al*. Early systemic cellular immune response in children and young adults receiving decellularized fresh allografts for pulmonary valve replacement. Tissue Eng Part A 2014;20:1003–11.

[11] Helder MR, Kouchoukos NT, Zehr K, Dearani JA, Maleszewski JJ, Leduc C *et al*. Late durability of decellularized allografts for aortic valve replacement: a word of caution. J Thorac Cardiovasc Surg 2016;152:1197–9.

[12] Sarikouch S, Haverich A, Pepper J, Pomar JL, Hazekamp M, Padalino M *et al*. Every like is not the same. J Thorac Cardiovasc Surg 2017;153:1553–5.

[13] Bando K. A proposal for prospective late outcome analysis of decellularized aortic valves. J Thorac Cardiovasc Surg 2016;152:1202–3.

[14] Cebotari S, Tudorache I, Ciubotaru A, Boethig D, Sarikouch S, Goerler A *et al*. Use of fresh decellularized allografts for pulmonary valve replacement may reduce the reoperation rate in children and young adults: early report. Circulation 2011;124:S115–23.

[15] Etnel JRG, Huygens SA, Grashuis P, Pekbay B, Papageorgiou G, Roos Hesselink JW *et al*. Bioprosthetic aortic valve replacement in nonelderly adults: a systematic review, meta-analysis, microsimulation. Circ Cardiovasc Qual Outcomes 2019;12:e005481.

[16] Etnel JRG, Grashuis P, Huygens SA, Pekbay B, Papageorgiou G, Helbing WA *et al*. The Ross procedure: a systematic review, meta-analysis, and microsimulation. Circ Cardiovasc Qual Outcomes 2018;11:e004748.

[17] David TE, Ouzounian M, David CM, Lafreniere-Roula M, Manlhiot C. Late results of the Ross procedure. J Thorac Cardiovasc Surg 2019;157:201–8.

[18] Naji P, Griffin BP, Sabik JF, Kusunose K, Asfahan F, Popovic ZB *et al*. Characteristics and outcomes of patients with severe bioprosthetic aortic valve stenosis undergoing redo surgical aortic valve replacement. Circulation 2015;132:1953–60.

[19] Mazine A, El-Hamamsy I, Verma S, Peterson MD, Bonow RO, Yacoub MH *et al*. Ross procedure in adults for cardiologists and cardiac surgeons: JACC state-of-the-art review. J Am Coll Cardiol 2018;72:2761–77.

[20] El-Hamamsy I, Eryigit Z, Stevens LM, Sarang Z, George R, Clark L, Melina G *et al*. Long-term outcomes after autograft versus homograft aortic root replacement in adults with aortic valve disease: a randomised controlled trial. Lancet 2010;376:524–31.

[21] David TE. More data on the Ross procedure. J Thorac Cardiovasc Surg 2019;157:142–3.

[22] Jassar AS, Desai ND, Kobrin D, Pochettino A, Vallabhajosyula P, Milewski RK *et al*. Outcomes of aortic root replacement after previous aortic root replacement: the "true" redo root. Ann Thorac Surg 2015;99:1601–8; discussion 1608–9.

[23] da Costa FD, Dohmen PM, Duarte D, von Glenn C, Lopes SV, Filho HH *et al*. Immunological and echocardiographic evaluation of decellularized versus cryopreserved allografts during the Ross operation. Eur J Cardiothorac Surg 2005;27:572–8.

[24] da Costa FD, Costa AC, Prestes R, Domanski AC, Balbi EM, Ferreira AD *et al*. The early and midterm function of decellularized aortic valve allografts. Ann Thorac Surg 2010;90:1854–60.

[25] Tudorache I, Calistru A, Baraki H, Meyer T, Hoffler K, Sarikouch S *et al*. Orthotopic replacement of aortic heart valves with tissue-engineered grafts. Tissue Eng Part A 2013;19:1686–94.

[26] Sarikouch S, Theodoridis K, Hilfiker A, Boethig D, Laufer GAM, Cebotari, S *et al*. Early Insight into *In vivo* recellularization of cell-free allogenic heart valves. Ann Thorac Surg 2019;108:581–9.

[27] Boethig D, Horke A, Hazekamp M, Meyns B, Rega F, Van Puyvelde J *et al*. A European study on decellularized homografts for pulmonary valve replacement: initial results from the prospective ESPOIR Trial and ESPOIR Registry data. Eur J Cardiothorac Surg 2019;56:503–9.

[28] Huygens SA, Rutten-van Mölken M, Noruzi A, Etnel JRG, Corro Ramos I, Bouten CVC *et al*. What is the potential of tissue-engineered pulmonary valves in children? Ann Thorac Surg 2019;107:1845–53.