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5-Year results from the prospective European multi-centre study on decellularized homografts for pulmonary valve replacement ESPOIR Trial and ESPOIR Registry data

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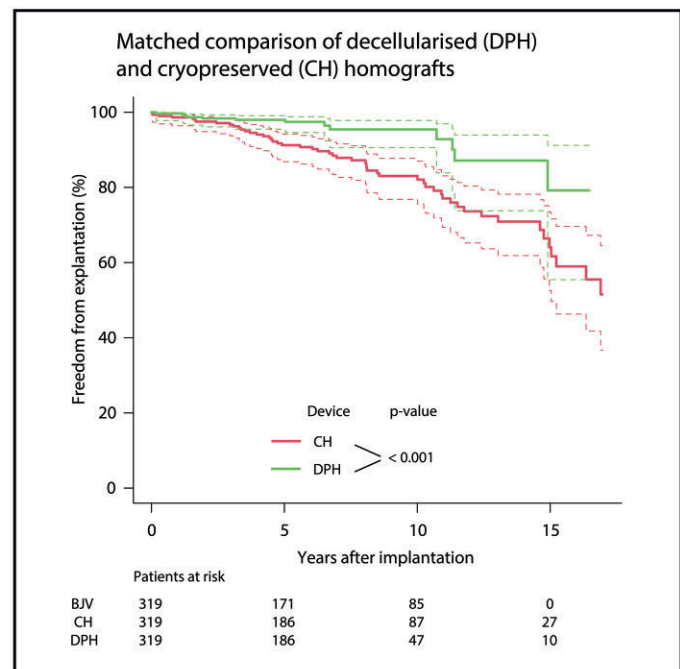
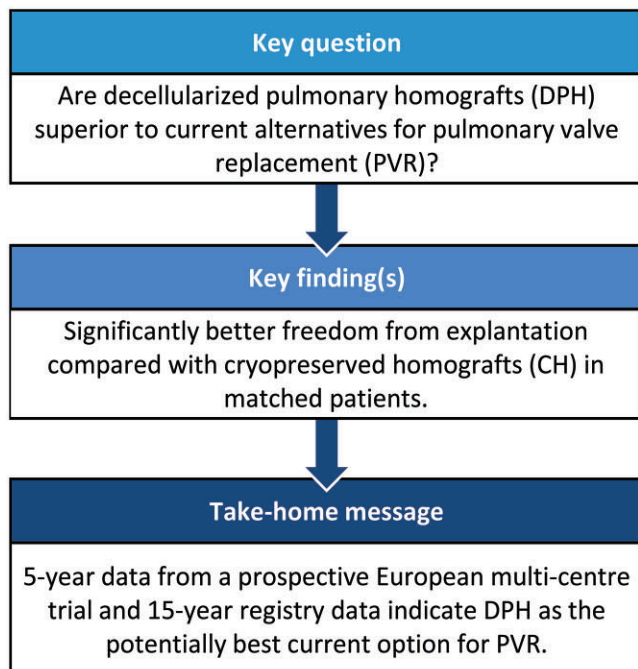
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Abstract

OBJECTIVES: Early results from the prospective ESPOIR Trial have indicated excellent results for pulmonary valve replacement using decellularized pulmonary homografts (DPH).

METHODS: A 5-year analysis of ESPOIR Trial patients was performed to provide an insight into the midterm DPH performance. ESPOIR Trial and Registry patients were matched with cryopreserved homografts (CH) patients considering patient age, type of heart defect and previous procedures to present the overall experience with DPH.

RESULTS: A total of 121 patients (59 female) were prospectively enrolled (8/2014–12/2016), median age 16.5 years (interquartile range 11.2–29.8), and median DPH diameter 24 mm. One death (73 year-old) occurred during a median follow-up of 5.9 years (5.4–6.4), in addition to 2 perioperative deaths resulting in an overall mortality rate of 2.5%. One case of endocarditis in 637 patient-years was noticed, resulting in an incidence of 0.15% per patient-year. At 5 years, the mean peak gradient was 19.9 mmHg (9.9), mean regurgitation 0.9 (0.6, grade 0–3) and freedom from explantation/any reintervention 97.5% (1.5). The combined DPH cohort, $n = 319$, comprising both Trial and Registry data, showed significantly better freedom from explantation for DPH 95.5% (standard deviation 1.7) than CH 83.0% (2.8) ($P < 0.001$) and less structural valve degeneration at 10 years when matched to 319 CH patients [DPH 65.5% (standard deviation 4.4) and CH 47.3% (3.7), $P = 0.11$].

CONCLUSIONS: The 5-year data of the prospective ESPOIR Trial show excellent performance for DPH and low rates of adverse events. ESPOIR Registry data up to 15 years, including a matched comparison with CH, demonstrated statistically significant better freedom from explantation.

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

ABBREVIATIONS

| | |
|-----|-------------------------------------|
| CH | Cryopreserved homografts |
| DPH | Decellularized pulmonary homografts |
| IQR | Interquartile range |
| PVR | Pulmonary valve replacement |
| SD | Standard deviation |

INTRODUCTION

Decellularized pulmonary homografts (DPH) for pulmonary valve replacement (PVR) have shown superior results to standard cryopreserved homografts (CH) in several single-centre analyses [1–3] as well as in a recent meta-analysis including the initial results of a prospective multicentre study on DPH, the ESPOIR Trial, funded by the European Commission [4].

Early data from this trial, which commenced in 2014, and from the ESPOIR Registry for patients who were operated on either before or outside the clinical study, were presented at the EACTS 2018 meeting in Milan. These initial findings demonstrated DPH to be safe and efficient in a multicentre setting, with excellent short-term haemodynamics. An analysis of over 700 patients following PVR showed DPH performance to be superior to other widely used options, such as bovine jugular vein conduits (Contegra®) and standard CH, in cohorts matched for age, type of congenital heart defect and the number of previous procedures [5].

A similar approach has been taken to analyse the results of decellularized aortic homografts (DAH) for aortic valve replacement. Early results from the ARISE trial were presented at the EACTS 2019 in Lisbon, together with a separate multicentre analysis of all paediatric aortic valve replacements [6]. Initial DAH results compared well with the early outcomes of contemporary Ross operation cohorts, despite the fact that DAH patients had undergone significantly more (>2×) previous cardiac procedures [7].

There is also emerging evidence that supports the presence of the desired recellularization of DPH and DAH by recipient cells. Substantial *in vivo* recellularization with non-inflammatory cells

was observed in a blinded standardized histological analysis of 11 decellularized homografts. This study, in addition to the study on paediatric DAH, however, demonstrated individual cases of early graft degeneration in decellularized homografts [8]. While the current findings did not point to the classic T-cell-mediated pathway for degeneration, there has been some evidence for an antibody-mediated mechanism. In a recent Dot-blot analysis in healthy controls, significant inter-individual differences were found in the binding of pre-formed antibodies to minced decellularized allografts [9]. Younger control persons showed significantly more antibody-binding than older controls and there was more antibody binding in aortic grafts. The most striking finding, however, was the significant variance in the reaction of individual healthy persons towards specific decellularized homografts, sometimes showing up to ten-fold more binding of preformed antibodies. Residual immunogenicity of decellularized homografts appears to exist despite the almost complete removal of cells, independent of ABO incompatibility and HLA constellation [10]. It is therefore of great interest to identify whether there is low-grade immune response in the long term and whether such a response can lead to an accelerated degeneration of DPH.

The aim of this study therefore is to (i) present 5-year data from the first European-wide prospective trial on DPH for PVR and (ii) summarize the current results for this specific DPH type in a matched direct comparison with CH.

MATERIALS AND METHODS

Ethics statement

The study was registered under ClinicalTrials.gov NCT 02035540 and initial results have been published at the respective ClinicalTrials.gov website. The study also received the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP®) seal as a Post Authorization Safety Study under Reference No. 5064 and is registered with the German authorities under Ref. Number NIS242 (www.espoir-clinicaltrial.eu). Approval was given by all local ethics committees (22.10.2013, No. 2016/2013–Hannover Medical

School Ethics Committee) before the start of the study, and informed consent was obtained appropriately from all participants or parents.

Study setting

The ESPOIR Trial received funding from the European Union's Seventh Framework Programme under Grant Agreement No. 278453 until 2019. Data collection following 2019 was financed by CORTISS GmbH, a Hannover-based non-profit organization for cardiovascular research (www.cortiss.de), Kleine Herzen Westerwald e.V. (www.kleine-herzen-westerwald.de), a patient organization for congenital heart defects in children, and by the participating institutions.

Indication for PVR according to current clinical guidelines was the key inclusion criterion without age limits; patients with active endocarditis were not included [11]. Surgical procedures were performed according to locally established standard procedures under cardiopulmonary bypass.

Homograft procurement and processing

Homografts were procured in line with current European Directives via 4 different tissue banks (European Homograft Bank, Dr. R. Jashari; German Society for Tissue Transplantation—DGFG, M. Börgel; Heart Valve Bank Beverwijk, A. van den Bogaerd; Fondazione Banca dei Tesutti di Treviso, Dr. A. Paolin) and shipped to Hannover for processing at Corlife oHG (www.corlife.eu).

Processing comprised ~30 individual steps using a detergent-based approach, as described previously, in accordance with German regulatory approval by the Paul Ehrlich Institute (www.pei.de, ESPOIR PV PEI.G.11634.01.1) [12]. This approval is recognized in most states in Europe.

Cohorts for matching

CH patients for matching were chosen from an updated RVOT Conduit Registry established by D. Boethig [13, 14], and DPH patients were matched to a CH patient. Matching was performed on the basis of the patient's age at implantation, the type of congenital heart defect, the number of previous operations and the number of previous PVR.

In 42 out of the 361 total patients with DPH, no match was found within the RVOT Conduit Registry, which reduced the number to 319 DPH patients for whom matches were available.

All 121 ESPOIR Trial patients were within the 319 DPH-matched patients. Propensity score analysis, to check whether this manual matching process was sufficient, was performed considering the age of the patient at implant (which also reflects the size of the implanted graft), the number of previous procedures and the number of previous PVR procedures. We found a mean difference of propensity scores of <1.3% (SE 0.5) between decellularized and CH. A Hosmer–Lemeshow test confirmed good comparability of the 2 groups with a *P*-value of 0.77.

Figure 1 provides a graphical overview of the study cohorts. Table 1 shows the characteristics of the 361 patients of the ESPOIR Registry and the 920 patients with conventional CH within the RVOT Conduit Registry before matching. Table 2 provides characteristics of the 2 study cohorts after the matching process.

Statistics

Summaries of the numeric data are given as the median and interquartile range (IQR) as well as means and standard deviation, also for not normally distributed data, to give an idea about the skewness. The Mann–Whitney *U*-test for non-paired samples was used for not normally distributed data, as assessed by the Kolmogorov–Smirnov test. Time-related events, such as freedom

Grant Agreement No. 278453



Study cohort -overview

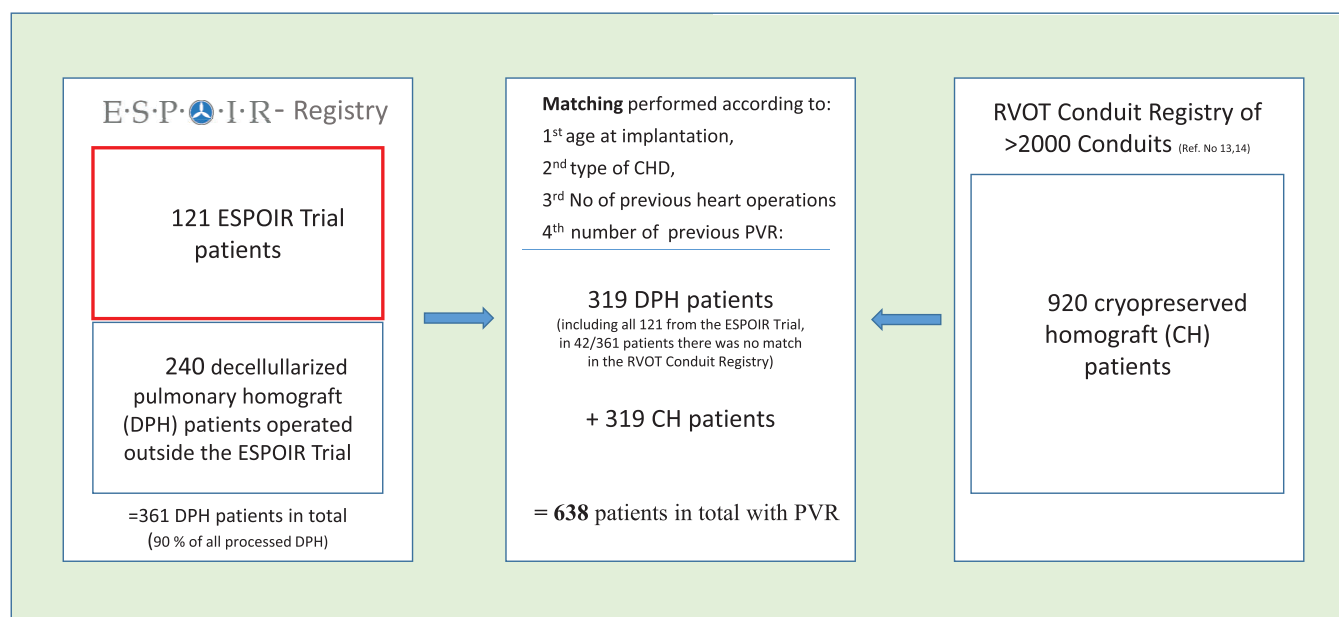


Figure 1: Graphical overview of the study cohort.

Table 1: Patient characteristics for the ESPOIR Trial and the ESPOIR Registry cohort, and the respective matched cryopreserved homograft and bovine jugular vein cohorts

| | ESPOIR Trial | ESPOIR Registry | RVOT Conduit Registry homografts |
|---|------------------|------------------|----------------------------------|
| Implantation period | 2014–2016 | 2005–2021 | 1982–2021 |
| Diagnoses (%) | | | |
| TOF | 44 | 43 | 113 |
| Ross | 21 | 14 | 580 |
| PI/PS | 14 | 13 | 25 |
| PA | 10 | 10 | 42 |
| DORV | 5 | 5 | 37 |
| TAC | 4 | 4 | 29 |
| TGA | 1 | 2 | 22 |
| Other | 1 | 9 | 72 |
| Total (n) | 121 | 361 | 920 |
| Median age at implantation, years (IQR) | 16.5 (11.2–29.8) | 16.4 (10.8–27.3) | 33.3 (12.8–48.0) |
| Median follow-up, years (IQR) | 5.9 (5.4–6.4) | 5.7 (2.6–7.8) | 7.7 (3.7–11.2) |
| Total follow-up (years) | 637 | 2011 | 7043 |
| Sex (male) | 61 (50%) | 231 (64%) | 644 (70%) |
| Number of previous operations | | | |
| 0 | 11 | 64 | 603 |
| 1 | 62 | 170 | 182 |
| 2 | 32 | 87 | 96 |
| >2 | 16 | 40 | 39 |
| Median conduit diameter (mm) (IQR) | 24 (23–26) | 25 (23–27) | 25 (23–27) |
| 12–19 (mm) | 6 | 25 | 75 |
| 20–23 (mm) | 37 | 104 | 199 |
| 24–29 (mm) | 78 | 232 | 621 |

IQR: interquartile range.

Table 2: Matched pairs

| | DPH | CH | CH versus DPH, P | Test |
|---|---------------|----------------|------------------|-------------|
| Implantation period | 2005–2021 | 1985–2021 | | |
| Diagnoses (%) | | | | |
| TOF | 45 | 35 | | |
| Ross | 13 | 34 | | |
| PI/PS | 14 | 6 | | |
| PA | 10 | 9 | | |
| DORV | 5 | 7 | | |
| TAC | 4 | 4 | | |
| TGA | 3 | 4 | | |
| Other | 6 | 1 | | |
| Total (n) | 319 | 319 | | |
| Mean age at implant. (years), mean ± SE | 19.1 ± 12.4 | 18.7 ± 13.1 | 0.63 | T (2-sided) |
| Median follow-up (years), (IQR) | 5.1 (3.9–7.3) | 6.5 (2.8–10.9) | <0.001 | MWU |
| Total follow-up (years) | 1408 | 2262 | – | |
| Number of prev. operations: 0 | 49 | 73 | 0.001 | MWU |
| 1 | 153 | 133 | | |
| 2 | 82 | 82 | | |
| >2 | 35 | 31 | | |
| Median conduit diam. (mm) (IQR) | 25 (23–27) | 24 (22–25) | 0.001 | MWU |
| 12–19 (mm) | 26 | 26 | | |
| 20–23 (mm) | 94 | 121 | | |
| 24–29 (mm) | 199 | 172 | | |

CH: cryopreserved homograft; DPH: decellularized pulmonary homografts; DORV: double outlet right ventricle; IQR: interquartile range; MWU: Mann-Whitney U-test; PA: pulmonary atresia; PI: pulmonary insufficiency; PS: pulmonary stenosis; TAC: truncus arteriosus communis; TGA: transposition of the great arteries; TOF: Tetralogy of Fallot.

from explantation and endocarditis, were evaluated according to Kaplan–Meier, including numbers at risk at 0, 5 and 10 years, as well as freedom from event rates at 0, 5 and 10 years, with their respective 95% confidence limits. For comparisons of such data, we applied log-rank tests.

The proportion of explanted and dysfunctional grafts over time was calculated for all 3 valve grafts as described above, with linear interpolation of the numerical values for peak gradients and insufficiency grades. The yearly status fractions were multiplied with the explantation rates observed at the end of entire post-implantation rates [3]. The Kruskal–Wallis test for independent samples with sorted hypotheses was applied to compare the fractions of intact conduits.

A peak echocardiographic gradient of ≥ 50 mmHg and regurgitation grade \geq moderate was defined as dysfunctional.

SPSS 23 (IBM Corporation, Somers, NY) was used for the analyses. No correction for multiple testing was performed. All the statistical tests were two-sided and a probability *P*-value of 0.05 or less was considered statistically significant.

RESULTS

5-Year results within the prospective ESPOIR Trial cohort

A total of 121 patients were prospectively enrolled in the ESPOIR Trial between August 2014 and December 2016 at 7 centres in Europe. The study has a 100% follow-up rate up to April 2021.

The median age at implantation was 16.5 years (IQR 11.2–29.8), and the median DPH diameter was 24 mm. Two perioperative deaths in adult congenital heart disease (GUCh) patients (30

and 59 years) had occurred due to postoperative myocardial failure after multi-valve procedures.

The oldest patient (73 years) included in the trial died 14 months after DPH implantation due to surgical complications arising from a proximal humerus fracture. The same patient underwent antibiotic treatment for suspected DPH endocarditis 8 months after DPH implantation as a small structure was attached to the otherwise completely normal valve. This structure, as well as the valve function, remained unchanged during further follow-up so that a bacterial endocarditis appears unlikely. No further mortality has been observed during a median follow-up of 5.9 years (IQR 5.4–6.4) in 637 patient-years, resulting in an overall mortality rate of 2.5%.

The primary efficacy end points at 5 years showed a mean peak gradient of 19.9 mmHg [standard deviation (SD) 9.9] and a mean regurgitation grade of 0.9 (SD 0.6, grade 0–3). One DPH was explanted after 23 months for technical reasons during reoperation for recurrent subvalvular stenosis caused by a pericardial patch. No further valves were explanted during follow-up. Three valve-related catheter interventions were performed. Two stents were implanted due to distal suture stenosis and 1 Melody[®] was implanted in a complex presentation with bilateral pulmonary branch stenosis. As outlined above, 1 case of endocarditis was documented over a total of 637 patient-years, resulting in an annual incidence for endocarditis of 0.15% per patient-year. At 5 years postintervention, freedom from explantation/any reintervention was 97.5% (SD 1.5).

Further characteristics of the ESPOIR Trial cohort are displayed in Tables 1 and 2. Kaplan–Meier curves showing freedom from death, endocarditis, conduit-related catheter interventions, explantation, explantation, catheter valve implantation, stenosis, regurgitation as well as freedom from combined degeneration and explantation are given in Fig. 2.

5-year-results of the ESPOIR Trial patients

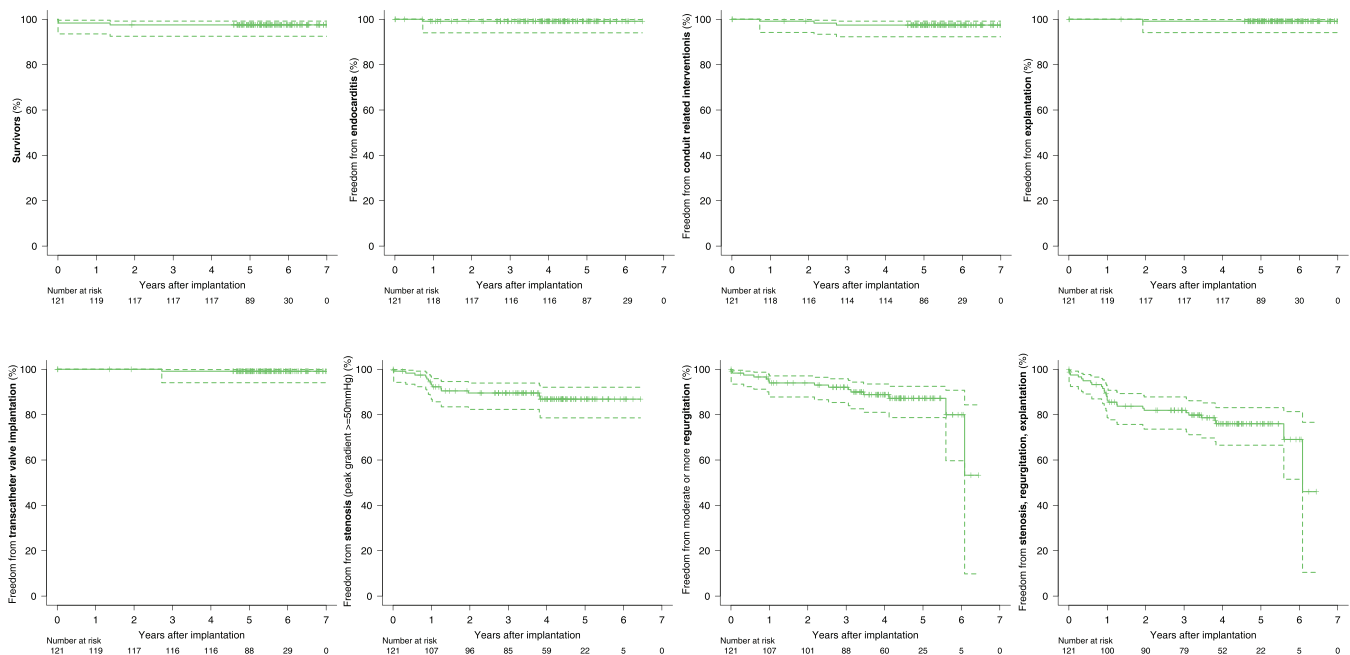


Figure 2: Kaplan–Meier curves showing freedom from death, endocarditis, conduit-related catheter interventions and explantation in the upper row for the ESPOIR Trial cohort. The lower row shows freedom from transcatheter valve implantation, stenosis, regurgitation as well as freedom from combined degeneration and explantation.

Results within the ESPOIR Registry over 15 years

The first implantations of DPH processed according the current decellularization protocol were undertaken in January 2005. The ESPOIR Registry aims to follow all patients with a DPH and currently contains data of 361 DPH implantations (including the ESPOIR Trial patients). This is 190% of all DPH processed by Corlife oHG.

The median age of the ESPOIR Registry patients is slightly lower than within the trial cohort with a median of 16.4 years (IQR 10.8–27.3). The DPH had a median diameter of 24 mm and the median follow-up period is 5.7 years (IQR 2.6–7.8).

At 5 and 10 years post-implantation, freedom from explantation/any reintervention was 97.2% (SD 0.9) and 95.6% (SD 1.5), respectively. The mean peak gradient across the pulmonary valve at 5 years was 22.6 mmHg (SD 14.6) and 31.1 mmHg (SD 19.1) at 10 years. Pulmonary regurgitation (Grade 0–3) at 5 years was 0.9 (SD 0.6) and 0.9 (SD 0.7) at 10 years. The incidence for endocarditis was 0.3% per patient-year.

Table 1 provides details for the ESPOIR Registry patients with respect to underlying cardiac malformations and previous cardiac operations, which are comparable with the ESPOIR Trial cohort. Figure 3 displays Kaplan–Meier analyses for freedom from death, endocarditis, conduit-related catheter interventions, explantation, catheter valve implantation, stenosis, regurgitation, as well as freedom from combined degeneration and explantation for a follow-up period of up to 15 years.

Outcome comparison of decellularized pulmonary homografts recipients (ESPOIR Trial and Registry patients) with matched cryopreserved homograft patients

To provide an overview of the current mid- to long-term DPH results, we performed a matched comparison of DPH to CH

using data from the updated RVOT Conduit Registry. We were able to match 319 DPH patients from the ESPOIR Registry as described above. All 121 ESPOIR Trial patients were included within this analysis. Fifty-six percentage of all patient data sets analysed were derived from the 7 centres participating in the ESPOIR study; the remaining were derived from 7 additional centres participating in the RVOT Registry.

Table 2 also provides details for each of the 2 study cohorts. Supplementary Material, Fig. SA shows almost identical conduit diameters in both homograft groups in relation to body weight.

The following analyses therefore are based on 319 DPH patients compared with matched 319 CH patients. There was no statistically significant difference in survival rates for the 2 homograft groups after 10 years. Figure 4 provides Kaplan–Meier analyses for freedom from death, endocarditis, conduit-related catheter interventions, explantation, catheter valve implantation, stenosis, regurgitation, and freedom from combined degeneration and explantation.

The combined DPH cohort, $n=319$, comprising both Trial and Registry data, showed significantly better freedom from explantation, DPH 95.5% (SD 1.7) than CH 83.0% (SD 2.8, $P < 0.01$), and less structural valve degeneration at 10 years when matched to 319 CH patients, DPH 65.5% (SD 4.4) and CH 47.3% (SD 3.7, $P = 0.11$).

Table 3 summarizes the specific results for each conduit type at 5 and 10 years.

Figure 5 gives an overview of freedom from explantation and the current functional status of the remaining conduits within each of the 2 matched groups. We also observed that the yearly summarized fractions of intact DPHs during all the commonly observed years were statistically significantly larger than the corresponding fractions of CHs (DPH versus CH, $P = 0.028$).

DISCUSSION

The procedure load for patients with congenital heart defects necessitating PVR still is very high, according to a recent large-

Outcome of all 361 DPH patients

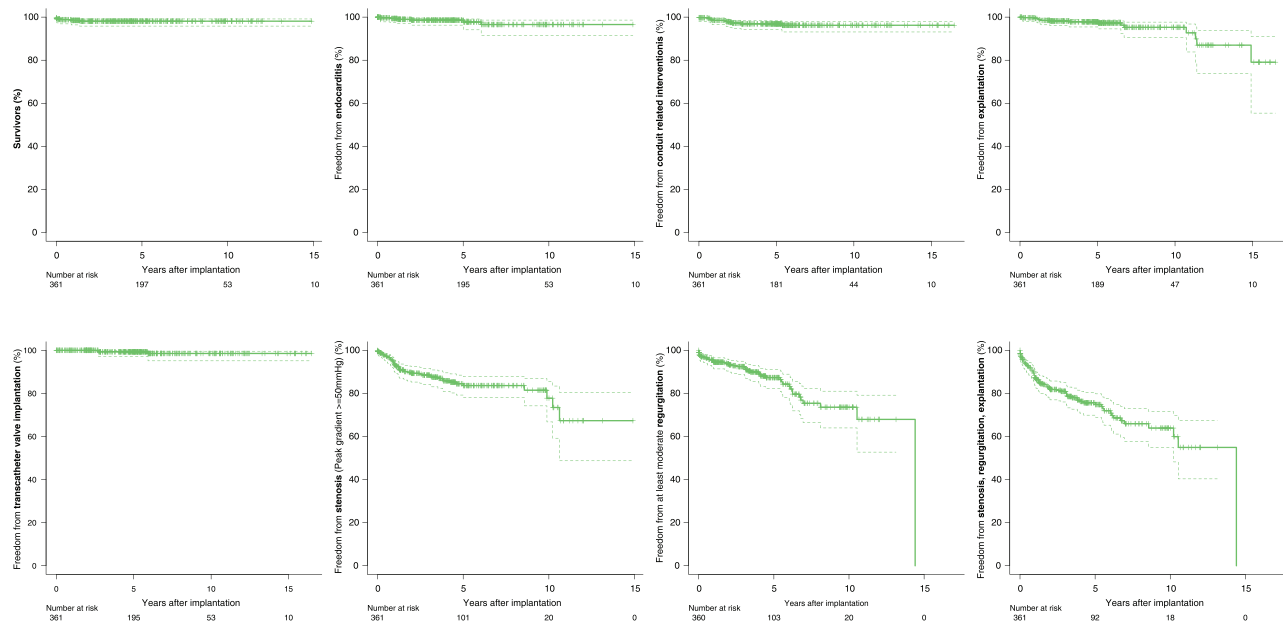


Figure 3: Kaplan–Meier curves showing freedom from death, endocarditis, conduit related catheter interventions and explantation in the upper row for the total ESPOIR Registry cohort ($n=361$), which includes the ESPOIR Trial patients. The lower row shows freedom from transcatheter valve implantation, stenosis, regurgitation and as well as freedom from combined degeneration and explantation for the ESPOIR Registry.

Matched comparisons of decellularised (DPH) and cryopreserved (CH) homografts

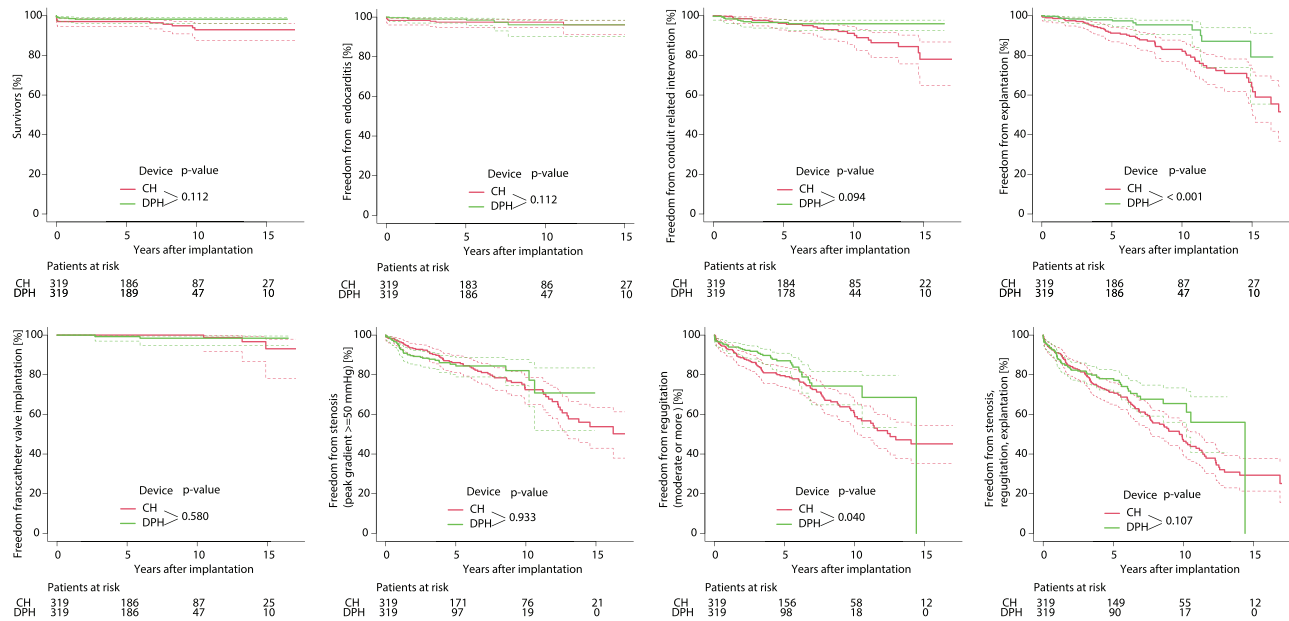


Figure 4: Kaplan-Meier curves for freedom from death, endocarditis, conduit-related catheter interventions, explantation are given in the upper row for matched cohorts of decellularized pulmonary homografts and conventional cryopreserved homografts. The lower row shows freedom from catheter valve implantation, stenosis, regurgitation, as well as freedom from combined degeneration and explantation. *P*-values for pairwise comparisons after 10 years are also given.

scale analysis of the German Competence Network for Congenital Heart Defects. At 30 years of age, 50% of the analysed patients underwent at least 5 procedures related to their right ventricular outflow tract, including at least 2 surgical PVR procedures [14]. This underlines the importance of prosthesis durability in PVR. The current analysis of the ESPOIR study data, to date the only prospective study on DPH, confirmed the excellent initial results. The 5-year analyses show very convincing data for freedom from death, functional or surgical valve explantation and endocarditis in a multicentre setting in Europe. No unexpected severe adverse events, such as graft rupture or late dehiscence, were observed.

This result is corroborated by analyses from the ESPOIR Registry, which comprises about 90% of all DPH processed according to the Hannover protocol. In the follow-up period covering up to 15 years postoperatively, the rate of explantation and endocarditis is also very low. A matched comparison of 319 DPH recipients with the 2 most widely used other options for PVR confirms that DPH can be considered as the current gold standard for PVR. This also holds true in meta-analyses, which combined data of different proprietary processing protocols for the decellularization of donated allografts [4]. Therefore, DPH have been convincingly demonstrated as superior to conventional cryopreserved pulmonary homografts and cannot be deemed to be merely a passing fashion, to cite an early editorial question raised at start of the ESPOIR Trial [15].

However, expectations that cell-free homografts may elicit a negligible immune response proved to be false, evidenced by increasing degeneration observed after 10 years. The most likely explanation is the activation of the recipient's immune system leading to tissue infiltration and tissue quality alteration. We have shown in an *in vitro* test system that there are marked differences in the binding of preformed antibodies towards various

decellularized human heart valves in the serum of healthy controls. This variance showed considerable inter-individual heterogeneity and up to ten-fold more binding of preformed antibodies in specific allograft-control serum combinations. Interestingly, only the age of the healthy control played a role and there was no observed impact resulting from donor age, ABO incompatibility and residual DNA content within the decellularized tissues [9]. No detectable HLA antibody response was observed after the implantation of decellularized valves in comparison with cryopreserved native allografts by Andreas *et al.* [10]. Currently, it remains unclear which epitopes within the decellularized allografts are the main leading agents of the initial immune system activation. The identification of these epitopes could open up the possibility of silencing to reduce immunization. We are also evaluating whether preoperative matching of patient and homograft using the described Dot-blot technique might offer an additional option to allay immune response.

Fortunately, cases in which the immunization leads to rapid degeneration with the need for repeat PVR within 2 years are extremely rare [8]. More commonly, the immune response appears to be mild, leading to a slow increase of stenosis over time. There are currently no good quality data available on whether any antithrombotic medication, which we would strongly recommend for the initial postoperative period given the above described potential immunogenicity despite complete decellularization, may be ceased or continued in the long term. The development of regurgitation appears to be evenly distributed over the first decade following implantation. After 10 years, the rate of degeneration increases, leading to a corresponding increase in explanted DPH. The limited number of explants to date does not allow a detailed assessment of whether a reduced rate of recellularization by non-immune competent recipient cells is a potential

Table 3: Freedom from diverse adverse outcomes in matched cohorts of 2 × 319 patients for decellularized pulmonary homografts and cryopreserved homograft

| Freedom from [%] | Conduit type | At 5 years mean (SD) | At 10 years mean (SD) | Pairwise comparisons (over full study period) |
|--|--------------|----------------------|-----------------------|---|
| Death | CH | 97.1 (1.0) | 92.9 (2.1) | } p=0.11 |
| | DPH | 98.1 (0.8) | 98.1 (0.8) | |
| Endocarditis | CH | 97.5 (1.0) | 97.5 (1.1) | } p=0.83 |
| | DPH | 98.5 (0.7) | 96.5 (1.6) | |
| Explantation | CH | 91.2 (1.8) | 83.0 (2.8) | } P<0.001 |
| | DPH | 98.0 (0.8) | 95.5 (1.7) | |
| Stenosis (> 50 mmHg peak) | CH | 86.1 (2.2) | 72.4 (3.4) | } p=0.93 |
| | DPH | 85.3 (2.3) | 82.1 (3.3) | |
| Regurgitation (≥ moderate) | CH | 79.5 (2.5) | 59.9 (3.9) | } p=0.04 |
| | DPH | 87.0 (2.3) | 74.3 (4.3) | |
| Degeneration (stenosis and regurgitation) | CH | 71.2 (2.8) | 47.3 (3.7) | } p=0.11 |
| | DPH | 78.0 (2.6) | 65.5 (4.4) | |

CH: cryopreserved homograft; DPH: decellularized pulmonary homografts; SD: standard deviation.

indicator for a failed regenerative heart valve strategy in these patients [8].

Interestingly, degeneration of decellularized homografts within the first 10 years following implantation did not lead to an increased risk for endocarditis. Freedom from endocarditis was

96.7% after 10 years. This stands in stark contrast to percutaneous valve replacement options, such as the Melody[®] valve. Here, the cumulative incidence of transcatheter pulmonary valve implantation infective endocarditis was 16.2% at 8 years of follow-up in a registry cohort of >800 patients with an almost identical age

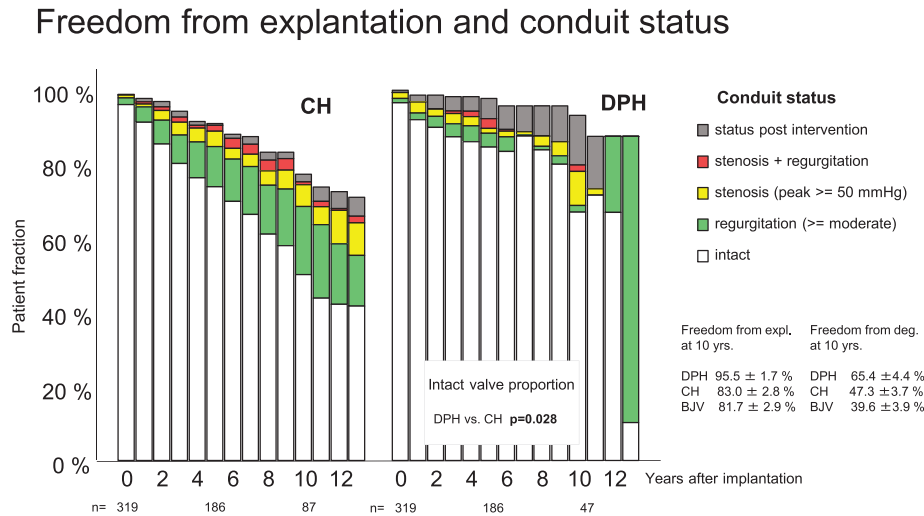


Figure 5: Freedom from explantation and functional conduit status for matched decellularized pulmonary homografts and cryopreserved homografts. We also analysed whether the yearly summarized fractions of intact decellularized pulmonary homografts during all the commonly observed years were larger than these fractions of cryopreserved homografts. Detailed pairwise comparisons including P-values are provided in Table 3.

composition and spectrum of underlying heart malformations [16]. The calculated annual risk per patient-year in Melody[®] is >7 times higher than in DPH. Therefore, it is our position that percutaneous PVR, at least using the Melody[®] valve, cannot be considered as a first-line treatment, given the substantial mortality rate from endocarditis [17].

While DPH appear to be the best currently available option for PVR in congenital heart disease, there remains the problem of reduced availability of homografts. The rate of heart valve donations has not significantly changed over the past 10 years in Western Europe [18]. Today, a significant number of pulmonary homografts are cryopreserved. Cryopreservation permits longer shelf times in comparison with current decellularization protocols and still serves a vital purpose in emergency situations. Nevertheless, in view of the superior durability of decellularized allografts, it may be wise to allocate more pulmonary allografts for decellularization to ensure an optimal use of this rare resource. A recent meta-analysis published by Johanna Takkenberg also showed the potential of Tissue-engineered pulmonary valves to be cost-effective despite the additional costs for processing [19].

In addition, experimental work is currently ongoing which aims at improved storage times of DPH by freeze-drying, which might present a solution to the problem of long-term preservation [20].

In the long run, decellularized xenogenic heart valves (DXH), derived from genetically modified animals, could help solve the question of availability [21]. Genetically modified DXH, on the other hand, require extended safety testing, thereby necessitating ethically delicate primate experiments, which have recently begun in a specialized research institution.

Limitations

The one-armed study design and the restrictions inherent in the manual matching process caused by low numbers and high

variance in congenital heart defects are the main limitations of this analysis, which nevertheless is one of the largest analyses of right ventricular outflow tract conduits to date.

Only retrospectively collected data were available for CH with sometimes incomplete data in echocardiographic reports. This, however, is likely to lead to an underestimation of valve degeneration and other adverse events in this cohort in comparison with the prospective follow-up for DPH patients.

For 4 (out of 12) patients based in Moldavia, follow-up was only possible by telephone due to the severe COVID-19 situation in 2020, which caused significant strain on the national health system. The COVID-19 pandemic also led to the delay of planned study examinations in other countries.

CONCLUSION

The 5-year data of the prospective ESPOIR Trial show excellent performance of DPH and low rates of adverse events. Data from the ESPOIR Registry up to 15 years, including matched comparison to conventional CH, demonstrate statistically significant better freedom from explantation or functional explantation for DPH.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

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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. Ramadan Jashari is a director of the European Homograft Bank. Martin Andreas has received institutional research funding (Edwards, Abbott, Medtronic, LSI) and has served as a proctor/speaker/consultant (Edwards, Abbott, Medtronic). Günther Laufer has received consulting fees from Edwards Lifesciences. All other authors declare that there are no conflicts of interest.

Data Availability Statement

The data underlying this article will be shared on reasonable request to the corresponding author.

Author contributions

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review & editing. **Axel Haverich:** Conceptualization; Data curation; Funding acquisition; Investigation; Project administration; Resources; Writing—review & editing. **Samir Sarikouch:** Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Writing—original draft.

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