



Cryopreserved human heart valve allografts: a ten-year single centre experience

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Abstract This study provides an overview of tissue banking activities at the Croatian Cardiovascular Tissue Bank (CTB) during past ten years and presents the outcomes of cryopreserved heart valve allografts (CHAs) use in different patient groups. From June 2011 until December 2021, 75 heart donations were referred to CTB: 41 recipient of heart transplant (RHT), 32 donors after brain death (DBD) and 2 donors after circulatory death (DCD) donations. Processing resulted in 103 valves of which 65 met quality requirements for clinical use. Overall tissue discard rate was 37%. The most frequent reasons for discard were inadequate morphology (12%) in

RHT donations and microbiological contamination (19%) in DBD donations. Altogether, 38 CHAs were transplanted to 36 patients. Recipients were divided in three groups; infective endocarditis (IE), non-infectious heart disease and congenital heart disease group. In the IE group, the 30-day, 1-year and 3-year survival was 71%, 53% and 47%, respectively. Freedom from re-operation due to all graft-related causes was 76% and due to structural valve deterioration 88%. There were no cases of graft reinfection. In the congenital heart disease group CHAs were predominantly (94%) used for right ventricular outflow tract reconstruction and 88% of patients recovered without graft-related complications. At present, the number of demands for CHAs at CTB considerably outweighs their availability.

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Introduction

The use of human heart valve allografts came into clinical practice during 1960s when Donald Ross and Brian Barratt-Boyes independently implanted cadaveric allograft in the aortic position (Ross 1962; Barratt-Boyes and Roche 1969). Despite initial success it soon became obvious that to ensure valve availability, allograft sterilization and preservation techniques

needed to be developed. In 1968 Barratt-Boyes proposed antibiotic treatment as a method of choice for allograft sterilization. At the same time, techniques such as freeze-drying, irradiation and glutaraldehyde pretreatment were too aggressive, and their use resulted in impaired allograft function (Hopkins 1989; Russo et al. 2017). Also, significant development in the field of mechanical and bioprosthetic valves additionally decreased the interest in allograft use until Marc O'Brien introduced cryopreservation in liquid nitrogen (LN₂) as a method for long-term storage of human tissues (O'Brien et al., 1987). This innovative method prompted new era of functional allograft storage that enabled development of tissue banks worldwide. Since then, tissue banks have advanced to establishments that are responsible for the procedures of donation, procurement, testing, processing, storage and distribution of tissues. Croatian Cardiovascular Tissue Bank (CTB) was founded in 2011 at the University Hospital Centre Zagreb (UHC Zagreb) with the aim to fulfill national demands for heart valve and vascular allografts. As a tertiary health care institution, UHC Zagreb provides advanced medical care and sophisticated medical procedures for various groups of patients. In that regard, immediately available allografts from CTB present additional treatment option for specific patient groups.

In comparison to other available heart valve substitutes, it has been shown that cryopreserved heart valve allografts (CHAs) exhibit natural biocompatibility, good hemodynamic profile, low risk of thromboembolic events and resistance to infection. However, during time several drawbacks of CHA use such as limited availability and propensity to structural deterioration came to light (Fukushima et al. 2014; Arabkhani et al. 2016; Poinot et al. 2018; Nappi et al. 2018, 2020). In addition, advances in development of artificial "off the shelf" prosthesis further limited their use. Nevertheless, CHAs are still invaluable treatment option for some patient groups. In patients with complex congenital heart diseases, CHAs are considered the first-choice valved conduits for reconstruction of right ventricular outflow tract (RVOT). They also present important part of surgical strategy for the treatment of infective endocarditis (IE), especially in the case of prosthetic valve endocarditis (PVE) with significant perivalvular extension of the disease which is associated with high mortality rate. Collecting the data about patient outcomes following

CHA implantation is crucial for evaluation of CHA long-term efficiency and durability. In this regard, the aim of this study was to provide an overview of CTB's banking activities during past ten years and to present the outcomes of CHA use in different patient groups.

Methods

Donor assessment

All heart donations referred to CTB from June 2011 until December 2021 were included in this study.

The organ or tissue donation from the deceased donors in Croatia is based on the opting-out system, which implies that the consent to donation is presumed if no objection to donation has been expressed by an individual during lifetime. However, if the family disagrees with the donation, their wishes would be respected, and organ or tissue procurement would not proceed. In the case of the living donation, patient's consent is always collected prior the procurement.

Most heart donations referred to CTB come from living donors (recipients of the heart transplant; RHT) and from deceased donors after brain death (DBD). Heart tissues from deceased donors after circulatory death (DCD) are usually not referred to CTB because hospitals in Croatia lack adequate premises for tissue procurement from this type of donors. However, in two instances DCD donations were accepted because in these cases, the donors were transferred to the operating theatre where proper environmental conditions for cardiovascular tissue retrieval could be achieved.

The acceptable age of the heart valve donors is between 32 weeks of gestation and 65 years. The donor eligibility for tissue donation is assessed by review of the available medical history, social/behavioural information, travel history and physical examination. Donor blood samples are used for haemodilution assessment and screening for blood transmissible diseases. Serological tests for HBV, HCV, HIV and syphilis and nucleic acid amplification technique (NAT) assays for HIV, HBV and HCV are always performed. In addition, seasonal NAT testing for West Nile Virus (WNV) is performed according to the current epidemiological guidelines. Also, since 2020 only donors with negative PCR test for SARS-CoV-2

obtained within 72 h before procurement can be accepted for donation. Additional donor blood samples are archived at CTB in case of a need for look back testing.

Tissue procurement and shipment to the CTB

All heart tissues are procured in the operating theatre by a trained surgical team. The procured heart is stored in 500 ml of saline transport solution in sterile triple layered package with wet ice. The donor's blood samples and tissue are then placed in transport container (Igloo, USA) loaded with 3 L of ice. Tissue needs to be delivered to CTB within 12 h.

Heart processing

The processing of the donated heart starts within 24 h from procurement. The processing is performed in a monitored cleanroom within the laminar flow cabinet with the background environment equivalent to the air quality Grade B according to the European Good Manufacturing Practice guidelines (EU GMP). The environmental microbiological monitoring is performed during all tissue processing steps.

Dissection of the heart is performed by a surgeon who is assisted by a CTB staff member. During the dissection, aortic valve with ascending aorta and pulmonary valve with pulmonary conduit with or without bifurcation are separated. The morphology of the tissues is thoroughly inspected. If abundant atheroma, fibrosis or calcifications in the vascular wall and/or leaflet basis are present, the tissue is discarded. The leaflets are also carefully examined to exclude the presence of large fenestrations that could influence valve competence. Leaflet coaptation is estimated using sterile Medium 199 (Gibco, USA). Briefly, after the valve conduit is filled with media thus performing the pressure on the valve, the degree of media leakage is evaluated as none, trivial, slight, moderate or severe. If trivial or no leakage is present, the valve is considered functional. However, if slight leakage is determined, the competence test should be repeated following decontamination procedure. In such cases, tissue is considered acceptable only if better results are obtained following repeated testing. If the leakage is estimated as moderate or severe, the valve is discarded. Finally, the valve diameters are measured by use of Hegar's dilators and the lengths of the aortic

and pulmonary conduits are recorded. The tissue is then submerged in the decontamination solution consisting of Medium 199 with antibiotics; vancomycin (50 µg/ml, Fresenius Kabi, Germany), lincomycin (120 µg/ml, Pfizer, USA) and polymyxin B (100 µg/ml, Caelo, Germany). Following the decontamination procedure at +4 °C for 24–48 h, tissue morphology is inspected again. Competence test and all measurements are repeated as well.

Following decontamination, tissue is rinsed in the sterile saline solution and immersed in cryoprotective solution comprised of 10% dimethyl sulphoxide (DMSO, Wak-Chemie, Germany) in sterile Medium 199 and cryopreserved according to the previously described validated protocol (Golemovic et al. 2022).

Collection of in-process quality controls

The initial tissue and transport solution, decontamination solution, rinsed tissue and cryoprotective solution are tested for the presence of aerobic and anaerobic bacteria, fungi and yeasts (BBL Thioglycollate Medium and BBL Trypticase Soy Broth, BD, USA). For liquid samples, 150 ml of the solution is tested by use of membrane filtration technique (S-Pak Filters 0.45 µm, Millipore, USA) while tissue samples are cut and directly inoculated into the culture media. All samples collected following decontamination procedure need to be sterile, if otherwise, allograft is discarded. If only initial tissue and transport solution test positive for microbiological contamination, the allograft outcome depends on the type of the microorganism detected. The list of microorganisms whose presence should result in tissue discard if detected at any stage of processing is defined in the CTB protocol. This list includes microorganisms suggested in the EDQM Guide to the quality and safety of tissues and cells for human application (EDQM 2019). However, based on CTB experience, this non-exhaustive list was supplemented with additional types of microorganism such as *Acinetobacter baumannii*, *Serratia marcescens* and *Proteus mirabilis*. In addition to the previously mentioned tissue and solution controls, microbiological swabs of the allograft primary package are taken as well (Transystem™ 108C Regular Rayon Swab with Amies Agar Gel, Copan, USA). The swab specimens are transported to the microbiology laboratory where they are immediately plated onto culture media plates that support the growth of

bacteria and fungi. The whole heart following valve isolation is sent for histopathological examination.

Medical release

The CHA remains in the quarantine until all results of the donor testing and in-process controls are collected. Finally, all testing results as well as the information about tissue donation, shipment, delivery, processing and storage are carefully reviewed by CTB medical director who makes a final decision about allograft outcome. All details of the process are recorded in handwritten forms and in customized software to ensure traceability. The CHAs designated as suitable for clinical application are stored in a separate LN2 vapour tank for up to 5 years.

Thawing procedure

The surgeon contacts CTB with a request for available tissues with characteristics suitable for a particular patient. On the day of the implantation procedure the tissue is transported to the operating theatre in the dry shipper at temperature below -135°C . The tissue is thawed according to the validated protocol as previously described (Golemovic et al. 2022). Thawed tissue must be kept at $+4^{\circ}\text{C}$ in sterile saline and be implanted within 6 h. The post-thaw tissue samples are sent for microbiological testing.

Patient population

Thirty-six patients who received CHAs distributed from CTB from June 2011 to December 2021 were included in this study. All patients were treated at the Department of Cardiac Surgery at UHC Zagreb. According to the etiology of the heart disease patients were divided in three groups; infective endocarditis (IE), non-infectious heart disease or congenital heart disease group. Patient demographic data and preoperative status were obtained through a retrospective review of medical records. In the group of patients who presented with infectious etiology, extensive review of all microbiological testing results was additionally performed. Preoperative blood culture results, duration of preoperative antibiotic treatment and intraoperatively detected microorganisms were included in this study. Operative details were

analyzed for all patient groups and they included the type of surgical procedure, duration of cardiac ischemia, cardiopulmonary bypass time and blood products input from the day of the allograft implantation until the patient discharge from the hospital. Data on blood products input were obtained from transfusion information system. General complications were defined as surgical re-exploration due to postoperative bleeding, atrioventricular block, post-cardiotomy extracorporeal membrane oxygenation (ECMO) support, respiratory insufficiency, renal failure and postoperative neurological dysfunction. Respiratory insufficiency was defined as need for mechanical ventilation longer than 48 h, renal failure as necessity for postoperative dialysis and neurological dysfunction as postoperative motoric deficit confirmed by neuroimaging methods. Details about postoperative outcomes were prospectively collected in the computerized database. The follow-up period was defined as the time elapsed from implantation of the allograft until the last clinical examination performed by cardiologist or the last telephone interview with the patient or the treating physician in the local hospital.

Biovigilance

A systematic monitoring of serious adverse reactions and events (SARE) from the donor selection to the recipient follow-up is implemented in the quality management system of CTB and UHC Zagreb. All non-compliances are documented in electronic and handwritten forms and reviewed by CTB medical director. In case that criteria for SARE is met, the incident is immediately reported to the Competent Authority (Ministry of Health) that evaluates the notification and intervenes appropriately. Competent Authority sends annual reports of SARE to the European Commission.

Results

Donors and allografts

From June 2011 until December 2021, 75 heart donations were referred to CTB from 11 different hospitals in Croatia (Table 1). Altogether, there were 41 RHT, 32 DBD and 2 DCD donations

Table 1 Donors of heart valves

Cause of transplantation/death	N	Gender male/female	Median age/years (min–max)
RHT	41	28/13	46
Dilated cardiomyopathy	31	23 / 8	47 (4–58)
Ischaemic cardiomyopathy	6	2 / 4	50 (35–57)
Restrictive cardiomyopathy ^a	4	3 / 1	22 (12–30)
DBD	32	14 / 18	47
Intracranial hemorrhage	21	9 / 12	49 (21–60)
Intracranial injury	5	3 / 2	38 (22–51)
Cardiac arrest	3	1 / 2	22, 49 and 1
Stroke, not specified as hemorrhage or infarction	1	1 / 0	49
Death due to intentional self-harm	1	0 / 1	12
Drowning	1	0 / 1	12
DCD	2	0 / 2	0
Birth asphyxia	2	0 / 2	0

^anot secondary to an infiltrative process

RHT recipient of heart transplant (living donor), *DBD* donor after brain death, *DCD* donor after circulatory death

(Table 2). The causes of transplantation in the case of RHT donations and causes of death in the case of DBD and DCD donations are listed in Table 1. The median time from the procurement until the storage of the tissue was 54 h 52 min.

Table 2 Processed tissues and reasons for discard of tissues

	Type of donation			Total
	RHT	DBD	DCD	
Procured hearts (n)	41	32	2	75
Processed hearts (n)	30	32	2	64
Processed tissues (n)	41	58	4	103
Discarded tissues (n)	15	22	1	38
Discard rate of processed tissues	37%	38%	25%	37%
<i>Reasons for processed tissue discard</i>	<i>RHT</i>	<i>DBD</i>	<i>DCD</i>	<i>Proportion in discarded tissues</i>
Morphology	5	7	1	34%
Microbiological contamination	1	11	/	32%
Medical contraindication	5	1	/	16%
Technical error	2	2	/	11%
Serology results	2	/	/	5%
Tissue damage inflicted during retrieval	/	1	/	3%

RHT recipient of heart transplant (living donor), *DBD* donor after brain death, *DCD* donor after circulatory death

RHT donations

Out of 41 RHT heart donations, 11 hearts (27%) were initially discarded (Fig. 1a). In these cases, extensive damage of the tissue inflicted during retrieval procedure resulted in no possibility to isolate functional valves. Out of the remaining 30 RHT hearts, 4 resulted in two, 18 in one and 8 in no valve allografts that met quality requirements (Fig. 1a). Altogether, in 54% of RHT donations (22/41) heart processing resulted in 26 allografts that met quality requirements. Total number of processed valves was 41 of which 15 were discarded (37%) (Table 2). The most frequent reasons for tissue discard were inadequate morphology (12%) and medical contraindication (12%). Altogether five valves originating from five different donors were discarded due to inadequate morphology and five valves from three different donors due to medical contraindications that were discovered following detailed investigation of donors’ medical history. Only one valve was discarded due to microbiological contamination of initial tissue sample and transport solution with *Pseudomonas aeruginosa*.

DBD donations

In the past ten years 70 DBD donations of cardiovascular tissues were referred to CTB and only 32 of them (46%) included heart donation. None of the hearts was discarded due to damage inflicted during

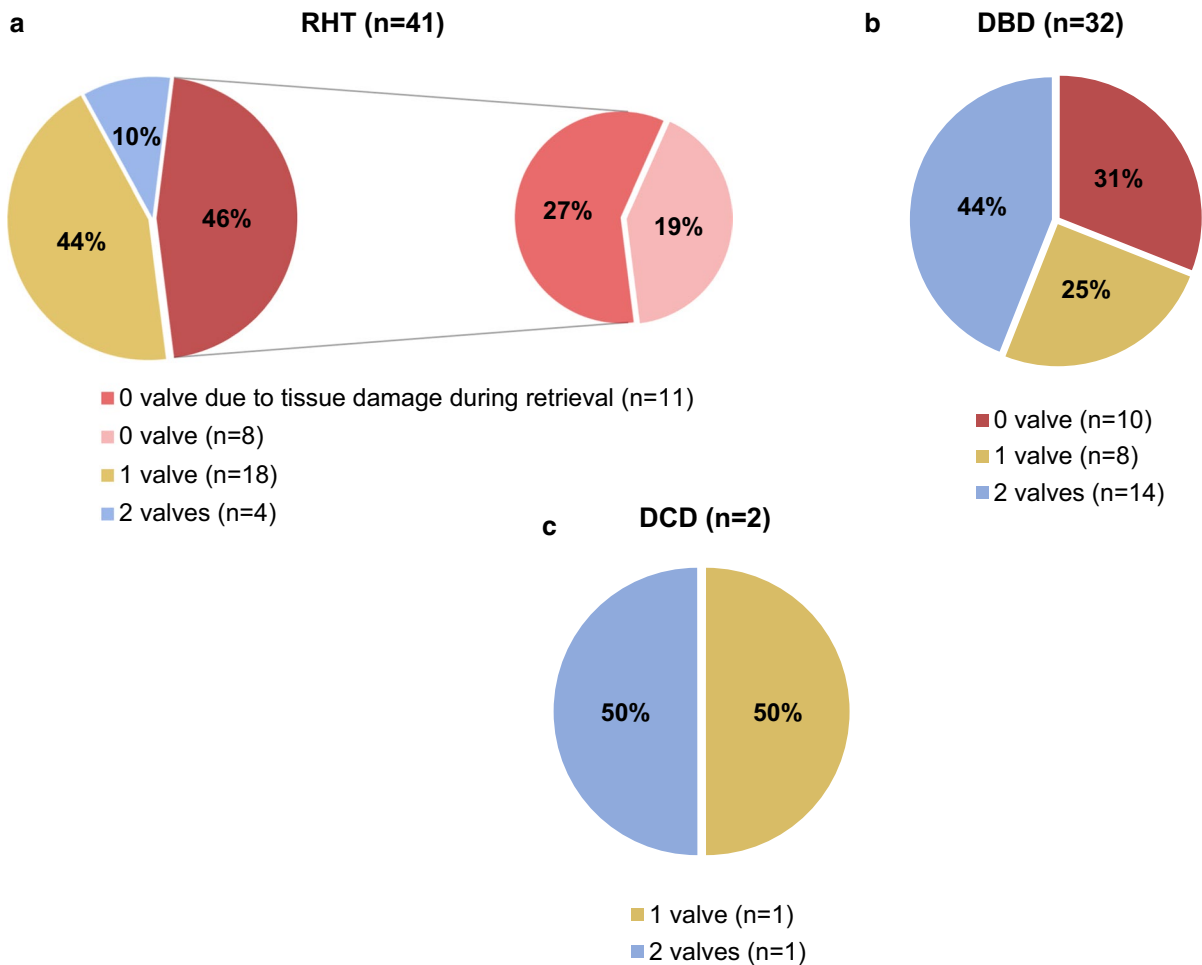


Fig. 1 Proportion of valves that met quality requirements for clinical use in different types of donations

retrieval procedure. Processing of 14 hearts resulted in two, 8 in one and 10 in no valve allografts that met quality requirements (Fig. 1b). Altogether, in 69% of DBD donations (22/32) heart processing resulted in 36 allografts that met quality requirements. In total, 58 valves were obtained by processing of which 22 were discarded (38%) (Table 2). The most frequent reasons for tissue discard were inadequate morphology (12%) and microbiological contamination (19%). Seven valves originating from six different donors were discarded due to inadequate morphology. Eleven valves originating from seven different donors were discarded due to microbiological contamination with microorganisms that, according to CTB criteria, if found at any stage of

processing should result in tissue discard. The following contaminants were detected in the initial tissue samples and transport solution: *Pseudomonas aeruginosa*, *Enterococcus faecalis*, *Candida spp* and *Acinetobacter baumannii*. Among these donations, in two cases *Candida spp* was identified in the initial sample (tissue and transport solution) and in the subsequent controls of all processed tissues as well (decontamination solution and rinsed tissue). However, in two cases when initial samples tested positive for *Enterococcus faecalis*, *Candida spp* was identified only in subsequent control samples. All tissues that were initially sterile, tested negative in subsequent controls as well.

DCD donations

There were only two DCD donations. Altogether, four valves were obtained by processing of which one was discarded due to inadequate morphology (Fig. 1c, Table 2).

Cryopreserved heart valve allografts

In summary, processing of all hearts received at CTB resulted in 103 valves of which 65 met quality requirements for clinical use. Overall tissue discard rate amounted 37% (Table 2). In total, 41 CHAs were distributed for transplantation. Two CHAs were thawed but not implanted because of surgeons' change of decision due to unexpected course of surgical intervention. One CHA was not removed from a monitored dry shipper and it was returned to CTB storage. Altogether 38 CHAs were used in 36 surgical procedures in the same number of patients (Table 3). The post-thaw tissue control samples were all sterile except in one case when CHA tested positive for *Coagulase Negative Staphylococcus*. The patient received appropriate antibiotic treatment and recovered without complications.

Infective endocarditis group of patients

A total of 17 patients with IE were included in the first group. Demographics and patient clinical data are listed in Table 4. The median age of patients was 57 (22–75). The indications for surgical procedure were aortic valve endocarditis ($n = 16$) and pulmonary valve endocarditis ($n = 1$, Fig. 2). Among patients with aortic valve endocarditis, 15 patients (94%) were operated due to PVE and one due to native valve endocarditis. Fifteen patients (88%) had significant

perivalvular extension of the disease, with aortic root abscess being the most commonly observed complication. Twelve patients (71%) presented with significant or severe heart failure symptoms according to the New York Heart Association classification (NYHA class III and IV). Infective endocarditis was predominately caused by *Staphylococcus species* (59%), followed by *Enterococcus faecalis* (24%) and *Streptococcus species* (12%). Four patients had more than one pathogenic microorganism present in blood cultures and/or intraoperative samples. Median duration of preoperative antibiotic treatment was 25 days (5–42). Altogether, 19 CHAs were transplanted (Table 3). In 15 procedures one allograft was used and in two cases two allografts were necessary to complete the procedure. The prevalent procedure was aortic root replacement (71%).

Treatment outcome

The median length of patients' postoperative stay in our centre was 15 days (0–70). Following discharge, most patients continued their postoperative care in the University Hospital for Infectious Diseases. The 30-day mortality rate was 29% (5/17 patients). One death during this period was graft-related, and it was caused by the rupture of aortic wall of implanted aortic valve allograft 29 days after surgery. The remaining deaths were non-graft-related, and they were mainly caused by myocardial failure. During early postoperative period respiratory insufficiency, renal failure, need for post-cardiotomy ECMO support and atrioventricular block were recorded in eight, six, five and three patients, respectively.

Table 3 Transplanted CHAs

No. of transplanted/distributed CHAs		38/41 (93%)	
Patient groups		Type of transplanted CHAs	N
Infective endocarditis	$n = 17$	Aortic valve with ascending aorta	18
		Pulmonary valve with main, left and right arteries	1
Non-infectious heart disease	$n = 3$	Aortic valve with ascending aorta	2
		Pulmonary valve with main, left and right arteries	1
Congenital heart disease	$n = 16$	Aortic valve with ascending aorta	6
		Pulmonary valve with main, left and right arteries	3
		Pulmonary valve with main artery	7

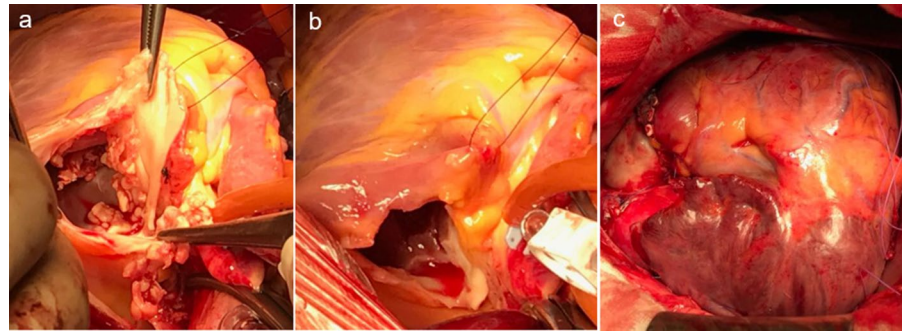
CHA cryopreserved human heart valve allograft

Table 4 Demographics and clinical data for the group of patients with infective endocarditis

Demographics	N
Total number of patients	17
Age (yrs; median, range)	57 (22–75)
Gender (male/female)	10/7
Indications	
Prosthetic valve endocarditis (<i>aortic/pulmonary</i>)	15 (15/0)
Native valve endocarditis (<i>aortic/pulmonary</i>)	2 (1/1)
Preoperative status	
<i>Prosthetic valve endocarditis</i>	15
Perivalvular complications (<i>Abscess/ Pseudoaneurysm/Fistulae</i>)	14 (12/3/1)
Septic embolism (<i>One/Multiple</i>)	2 (1/1)
AV block	1
<i>Native valve endocarditis</i>	2
Perivalvular complications (<i>Pseudoaneurysm</i>)	1
AV block	1
Comorbidities	
Hypertension	10
Hyperlipidemia	8
Obesity	5
Renal insufficiency	3
Causative microorganisms	
<i>Staphylococcus sp.</i>	10
<i>Staphylococcus aureus/ Staphylococcus epidermidis/Staphylococcus sp./MR-CoNS</i>	4/3/2/1
<i>Enterococcus faecalis</i>	4
<i>Streptococcus sp.</i>	2
<i>Streptococcus sp. (BHS group D)/Streptococcus gallolyticus</i>	1/1
<i>Enterobacter spp. ESBL</i>	1
<i>Pseudomonas aeruginosa</i>	1
<i>Acinetobacter baumannii</i>	1
<i>Cutibacterium acnes</i>	1
Blood-culture negative	3
Operative data	
Total number of procedures (ARR/AVR/AAR/RVOT reconstruction)	17 (12/5/3/1) ^a
Cardiopulmonary bypass time (min; median, range)	386 (100–540)
Cardiac ischemia (min; median, range)	251 (73–375)
Blood products input (total number of units; median)	53 (14–152)
RBC (number of units; median)	21 (6–60)
FFP (number of units; median)	13 (4–31)
Platelets (number of units; median)	20 (4–67)
Donor-recipient blood group match (N, %)	8 (42,1)
Postoperative data	
ICU stay (days; median, range)	11 (0–70)
Postoperative hospital stay (days; median, range)	15 (0–70)

^a in two procedures two homografts were used for reconstruction and in additional two procedures one homograft was used to perform ARR and AAR simultaneously
 AV atrioventricular, MR-CoNS Methicillin-resistant coagulase-negative Staphylococcus, ARR aortic root replacement, AVR aortic valve replacement, AAR ascending aorta replacement, RVOT right ventricular outflow tract; RBC red blood cells, FFP fresh frozen plasma

Fig. 2 Native pulmonary valve endocarditis in a 37-year-old patient (a). After complete excision of the infected tissue (b) reconstruction was performed using pulmonary valve allograft with main pulmonary artery (c)



The median length of follow-up of patients ($n=12$) who survived 30-day postoperative period was 40 months (2–89). During first postoperative year three additional deaths were recorded. One patient died due to myocardial infarction, while in the case of the remaining two patients the actual cause of death was not determined. One patient died during second postoperative year due to hematological disorder. The 1- and 3-year survival rates were 53% and 47%, respectively.

During complete follow-up period four patients needed re-operation due to graft-related complications. Two of these re-operations were necessary during early postoperative period. As previously mentioned, one patient died due to rupture of aortic wall of implanted aortic valve allograft. In the case of the second patient, anastomotic disruption between allograft and native aorta caused significant bleeding that required urgent chest re-exploration. This patient successfully recovered. The remaining two re-operations were necessary during late follow-up period due to structural valve deterioration. First patient presented with severe mixed aortic valve disease 4 years and 4 months after CHA implantation. In this case replacement of the allograft with mechanical valve was performed. In the case of the second patient pseudoaneurysm of the ascending aorta graft was detected 7 years and 5 months following aortic allograft implantation. The ascending aorta allograft was successfully replaced with Dacron prosthesis. In total, overall freedom from re-operation due to all graft-related causes was 76%, while freedom from re-operation due to structural valve deterioration was 88%. There were no cases of graft reinfection. At the latest follow-up contact, the remaining six patients were alive and free from intervention.

Non-infectious heart disease group of patients

The second group included three patients with non-infectious heart diseases. Patients' demographics and clinical data are listed in Table 5. The median age of patients was 66 (60–74). The indications for surgical procedure were aortic stenosis ($n=2$) and pulmonary artery angiosarcoma ($n=1$, Fig. 3). Altogether, three CHAs were transplanted (Table 3). There were no early deaths or graft-related complications in this group.

Treatment outcome

The median duration of postoperative stay was 12 days (5–32). The duration of follow-up for three patients was 1, 24 and 92 months, respectively. One patient was lost for follow-up after hospital discharge and one patient died two years following allograft implantation due to relapse and progression of pulmonary angiosarcoma. The remaining patient recovered without complications.

Congenital heart disease group of patients

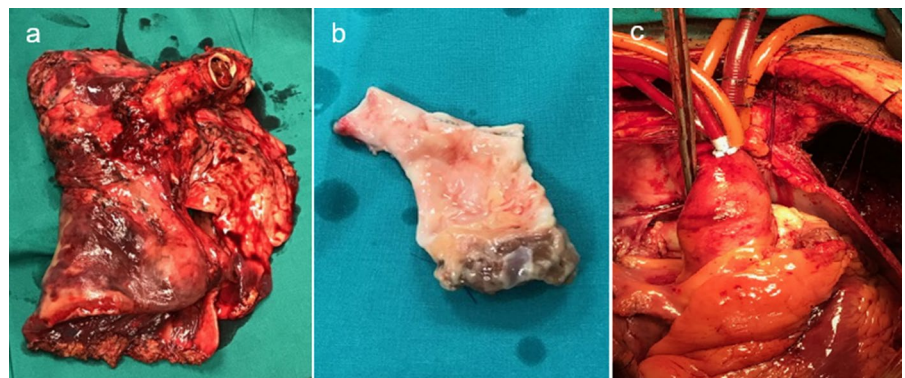
The third group included 16 patients who received allograft for the repair of congenital heart defects. The median age of patients was 11 (0–26). The indications for surgical procedure were pulmonary stenosis ($n=5$), pulmonary atresia ($n=3$), truncus arteriosus ($n=3$), aortic stenosis ($n=3$) and pulmonary valve insufficiency ($n=2$). Details about patient age, operative details and postoperative data are listed in Table 6. In six patients CHA was used for primary correction of congenital heart defect. These cases included three neonates with truncus arteriosus, two neonates with pulmonary atresia and one 20-year-old

Table 5 Demographics and clinical data for the group of patients with non-infectious heart disease

Demographics	N
Total number of patients	3
Age (yrs; median, range)	66 (60–74)
Gender (male/female)	0/3
Indications	N
Aortic stenosis	2
Pulmonary artery angiosarcoma	1
Comorbidities	N
Hypertension	2
Hyperlipidemia	2
Obesity	1
Smoking	1
Prior neurological event (stroke or TIA)	1
Operative data	N
Total number of procedures (AVR/RVOT reconstruction)	3 (2/1)
Cardiopulmonary bypass time (min; median, range)	174 (146–201)
Cardiac ischemia (min; median, range)	126 (114–138)
Blood products input (total number of units; median)	6 (5–10)
RBC (number of units; median)	4 (3–6)
FFP (number of units; median)	2 (2–4)
Platelets (number of units; median)	0
Donor-recipient blood group match (N, %)	1 (33,3)
Postoperative data	N
ICU stay (days; median, range)	1 (1–3)
Postoperative hospital stay (days; median, range)	12 (6–33)

TIA transient ischemic attack, AVR aortic valve replacement, RVOT right ventricular outflow tract, RBC red blood cells, FFP fresh frozen plasma

Fig. 3 Pulmonary artery angiosarcoma in a 60-year-old patient. The patient underwent left-sided pneumonectomy and resection of the left pulmonary artery with corresponding valve (a). Pulmonary valve allograft with main and left pulmonary artery (b) was used for reconstruction (c)



patient with Turner Syndrome and bicuspid aortic valve (BAV) who developed aortic stenosis. In one neonate with pulmonary atresia, hypoplastic pulmonary artery was palliated using allograft patch.

In the remaining nine patients, allograft implantation was second ($n=5$), third ($n=3$) or fourth ($n=1$) reoperation. The use of CHA in a neonate with pulmonary atresia with ventricular septal defect and

Table 6 Demographics and clinical data for the group of patients with congenital heart diseases

Demographics	N
Total number of patients	16
Age (yrs; median, range)	11 (0–26)
Neonates/Infants/Children/Adolescents/ACHD	4/2/2/6/2
Gender (male/female)	7/9
Indications	N
Pulmonary stenosis (w or w/o insufficiency)	5
Pulmonary atresia	3
Truncus arteriosus	3
Aortic stenosis (w or w/o insufficiency)	3
Pulmonary valve insufficiency	2
Operative data	N
Total number of procedures (Primary correction/Reoperation /Patch)	16 (6/9/1)
Extraanatomical position of the homograft	5
Cardiopulmonary bypass time (min; median, range)	237 (77–288)
Cardiac ischemia (min; median, range)	148 (97–206)
Blood products input (total number of units; median)	11 (4–17)
RBC (number of units; median)	3 (0–8)
FFP (number of units; median)	3 (1–5)
Platelets (number of units; median)	4 (0–12)
Donor-recipient blood group match (N, %)	5 (31%)
Postoperative data	N
ICU stay (days; median, range)	5 (2–34)
Postoperative hospital stay (days; median, range)	20 (7–38)

ACHD adult congenital heart disease, *RBC* red blood cells, *FFP* fresh frozen plasma

major aortopulmonary collateral arteries (PA/VSD/MAPCA) is presented in Fig. 4. Altogether, 16 CHAs were transplanted (Table 3). In total, 15 RVOT

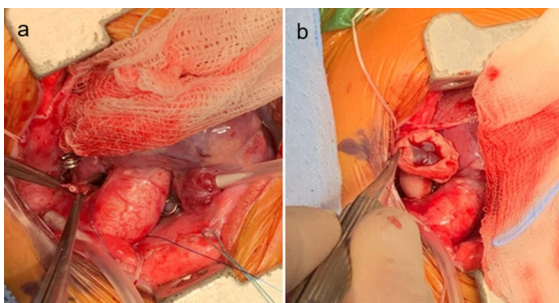


Fig. 4 Pulmonary atresia with ventricular septal defect and major aortopulmonary collateral arteries (PA/VSD/MAPCA) in a neonate patient. Rehabilitation of hypoplastic native pulmonary artery (a) was performed with an aortic valve allograft with ascending aorta used as a right ventricle-to-pulmonary artery conduit (b)

reconstructions and one aortic valve replacement (AVR) were performed. In five procedures allografts were implanted in the extra-anatomical position. In these cases, AV allografts were used to reestablish right ventricle (RV) to pulmonary artery (PA) continuity.

Treatment outcome

The median length of postoperative stay was 20 days (7–38). One case of hemothorax that required surgical re-exploration was recorded. The patient successfully recovered. There were no other early complications in this group of patients. The median duration of follow-up was 18 months (2–80). One patient who was referred to our centre from a neighboring country was lost for follow-up after 7 months. As expected in this group of patients, re-operation was necessary in two neonates. In the first case allograft patch was removed during complete correction procedure performed

when patient was 9 months old. In the case of the second patient significant stenosis of the pulmonary allograft conduit was determined 29 months after reconstruction. In this case allograft was replaced with Contegra® conduit. The remaining fourteen patients did not have graft-related complications during available follow-up.

Biovigilance activity

There were no cases of SARE during observed period. In this regard, the case of a patient with infective endocarditis who died on 29th postoperative day due to rupture of aortic wall of implanted aortic valve allograft was carefully examined. However, in this case SAR could not be attributed to the graft quality and was unequivocally excluded since there was clear evidence that the rupture of the aortic wall was a secondary effect of postoperative mediastinitis and related necessary surgical interventions.

Discussion

When the numbers of the heart valves processed and stored at CTB on the annual basis are compared with other European tissue banks, it is obvious that the CTB is relatively small cardiovascular tissue bank. However, all issues concerning the cardiovascular tissue banking are mirrored in this bank as well. The CTB primarily copes with inadequate donor availability which results in inability to fulfill all demands from local surgeons. Since CTB is located at the UHC Zagreb which is also a heart transplantation center, the shortage of DBD donations tried to be compensated by an increase in inflow of RHT donations. However, the difference in the successful allograft retrieval between DBD and RHT donations is well known (Jashari et al. 2010). Eleven out of 41 RHT hearts (27%) received at CTB were initially rejected due to tissue damage done during procurement. These events were more frequent at the beginning of the CTB activity and in time, following intense communication with transplant surgeons, the rate of hearts with iatrogenic damage significantly decreased. In addition to rejections due to tissue damage during procurement, the characteristics of RHT donors additionally contributed to the fact that 46% of all RHT donations

resulted in no allografts while in DBD donations this rate amounted 31% (Fig. 1). The majority of the remaining RHT donations resulted in only 1 valve while the majority of DBD donations resulted in 2 valves pointing out DBD donations as a more abundant tissue source (Fig. 1).

The median age of RHT and DBD donors was 46 and 47 years, respectively, which represents rather young population of donors. When CTB was established, the accepted upper age of donors was lower than today, and it changed in time according to the commonly accepted age limits in other cardiovascular tissue establishments (EDQM 2019) and the results of published studies (Grosse et al. 2008; Burkert et al. 2021). The younger age of our donor population is reflected in lower tissue discard rate due to morphological quality which is the discard reason strongly related to the donor's age. Only 34% (13/38) of valves were discarded due to morphological reasons (Table 2) which is quite low in comparison with other tissue establishments where this rate amounts 60–70% (Axelsson et al. 2021; Jashari 2021). In those banks inflow of the donated hearts is more abundant, and the donor age limit was raised some time ago which finally led to high discard rate due to morphological changes. In the case of CTB that copes with inadequate availability of tissue donors it is even more important that the morphology of the received tissues is assessed in a rational way. This implies that tissues with minor morphological changes, such as valves with small fenestrations that do not interfere with valve coaptation, can still be accepted.

In addition to inadequate morphology, another frequent reason for valve discard at CTB was initial microbiological contamination with highly virulent microorganisms. The rate of tissues discarded due to this reason amounted 32% (12/38) and it was more pronounced in the DBD group of donors (Table 2). Although RHT and DBD heart retrievals are both performed in the operating theatres, the setting and the timing of heart procurement in these two types of donations significantly vary. In the case of RHT donors, the thoracic cavity is completely isolated from the abdominal cavity. The heart tissue is retrieved fast because the surgeons are focused on cardiac transplantation and retrieved tissue is only shortly exposed to the environment before final packaging. On the other hand, in DBD donations, abdominal organs are retrieved prior to the heart which, in addition to

longer tissue exposure to the environment, increases risk of initial tissue contamination. These differences in the procurement procedures were reflected in the fact that in RHT donors, only one donation resulted in one valve discard while in the case of DBD donors seven separate donations resulted in valves' discard due to contamination with highly virulent microorganisms. The list of pathogens whose presence in any of the tested samples results in tissue discard is defined in the CTB protocol. Apart from the microorganisms listed in the recommendations for processing of cardiovascular tissue published in EDQM Guide (EDQM 2019), the CTB list incorporates some additional pathogens due to their clinical significance and high occurrence in our procurement facilities. Unfortunately, most tissue establishments do not make their pathogen-specific rejection criteria publicly available, which hinders reliable comparison of tissue discard rates among banks.

All CHAs that were distributed from CTB in the past 10 years were transplanted to the patients treated at the Department of Cardiac Surgery at UHC Zagreb. This close collaboration within the same institution enabled prospective collection of patient follow-up data and immediate communication on any non-compliances. The present study provides the results of CHA use in three different groups of patients and therefore procedure outcomes need to be discussed separately.

The most complex patients were those in the IE group since they presented with acute, rapidly progressive infection and life-threatening condition. The timing of surgical intervention and the ideal valve substitute for such patients are not strictly defined in The European Society of Cardiology (ESC) guidelines for the management of IE (Habib et al. 2015). These guidelines do not favor any specific valve substitute but recommend a tailored approach for each individual patient and clinical situation (Habib et al. 2015). Nevertheless, some pivotal studies have shown that CHAs exhibit better biocompatibility and resistance to infection and enable easier reconstruction, especially in the presence of aortic root abscess, in comparison to the conventional mechanical and bioprosthetic valve substitutes (Musci et al. 2010a, b; Yankah et al. 2002). The ESC guidelines also define the major predictors of poor outcome in patients with IE such as PVE, perivalvular complications, heart failure (NYHA class III or IV) and *Staphylococcus*

aureus as causative microorganism, which were present in 88%, 88%, 71% and 24% of our patients, respectively. Furthermore, pseudoaneurysms, prosthesis dehiscence and fistulae, that are all known to be associated with very severe valvular and perivalvular damage (Habib et al. 2015), were present in 18%, 12% and 6% of our patients, respectively. The 30-day, 1-year and 3-year survival rates in the IE group were 71%, 53% and 47%, respectively. These results are in accordance with the outcomes reported by some centers that, as UHC Zagreb, treat the most complex IE patient cases (Musci et al. 2010a, b). Such patients are often admitted with heart failure, renal failure or uncontrolled infection following failed antibiotic treatment and, in these cases, immediate surgical intervention is often required. International working group on IE indicated late referral of advanced stage IE patients to specialized centers as an important issue influencing patients' outcome (Chambers et al. 2014). It must be noted that although the average IE in-hospital mortality is about 20%, it may be as high as 79% if complicated cases are considered (Habib et al. 2015; Chambers et al. 2014). Therefore, the overall CHA implantation results of different centers must be interpreted in view of these factors. It also must be emphasized that surgical procedure is only one step in the treatment of IE. The long-term patient outcome is influenced by multiple factors such as adequacy of postoperative antibiotic treatment and management of postoperative complications. Multicenter studies still report 1-year mortality of approximately 40% for the diagnosis of IE (Pettersson and Hussain, 2019). In that regard, treatment of complicated IE remains challenging and long-term postoperative surveillance of these patients is necessary (David et al. 2007).

The second important part of patient results presented in this study refers to the use of CHA for the repair of complex congenital heart defects. In this patient group CHAs were used for primary correction of congenital heart defects or re-operation due to previous conduit's degeneration. In 94% of procedures CHAs were used for reconstruction of RVOT. Taken together, satisfactory early results have been accomplished and 88% of patients recovered without complications during available follow-up. In one neonate, allograft replacement was necessary 29 months following implantation due to significant stenosis of the conduit. In this patient multiple risk factors that

adversely affect graft longevity were present including truncus arteriosus, young age and low weight at implantation, smaller allograft diameter and extra-anatomical position of the allograft (Tweddell et al. 2000; Rodefeld et al. 2008; Boethig et al. 2007). It has recently been reported that freedom from re-intervention during first decade following allograft use for reconstruction of RVOT in patients with congenital heart diseases ranges from 75 to 82% (Axelsson et al. 2021; Willetts et al. 2021; Dekens et al. 2019). However, these values are expected to be around 50% in younger recipients in whom smaller diameter allografts are used (Boethig et al. 2007). It is possible that these aspects contributed to the early allograft degeneration in our patient's case. Due to short follow-up of patients presented in this study it is obvious that our results cannot be compared with previously mentioned outcomes. Nevertheless, promising early results of CHA use in this patient group have significantly increased the interest of pediatric cardiac surgeons at our institution for this type of conduit. As a consequence, since 2020 the number of demands for allografts at CTB considerably outweighs their availability.

In conclusion, the present study provided an overview of the results accomplished in banking and use of CHAs during ten years of CTB activity. The main issues concerning the cardiovascular tissue banking have been discussed. The presented patients' outcomes following use of CHAs need to be interpreted in view of limitations of this study. This primarily refers to the small size of the patient groups and heterogenous patients' characteristics which implies that results hold no statistical significance. Nevertheless, since the ideal valve substitute, that would have an excellent hemodynamic profile and would be free from structural degeneration and need for anticoagulation therapy is still not available, all allograft-related experience presents valuable data.

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Author contributions Study conception and design: MS, MG. Acquisition of data: MS, MG, IS, ZD. Analysis and interpretation of data: MS, MG, IS, ZD. Drafting of manuscript:

MS, MG. Critical revision of manuscript: MS, MG, IS, ZD, BB, BGC.

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Data availability The data sets generated and analysed during this study are not publicly available due to protection of patients' and tissue donors' personal data but are available from the corresponding author on reasonable request.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval All procedures in this study were performed in accordance with the ethical standards of the 1964 Helsinki declaration and its later amendments. The study was approved by the Ethical committee of the University Hospital Centre Zagreb (reference number 8.1–22/61–2).

Informed consent Informed consent was obtained from tissue donors or their next of kin.

References

- Arabkhani B, Bekkers JA, Andrinopoulou E-R, Roos-Hesselink JW, Takkenberg JJM, Bogers AJJC (2016) Allografts in aortic position: insights from a 27-year, single-center prospective study. *J Thorac Cardiovasc Surg* 152:1572–1579. e3. <https://doi.org/10.1016/j.jtcvs.2016.08.013>
- Axelsson I, Malm T, Nilsson J (2021) Impact of valve fenestrations and structural changes in homografts on the long-term outcome in the recipient. *Cell Tissue Bank* 22:399–408. <https://doi.org/10.1007/s10561-020-09886-5>
- Barratt-Boyes BG, Roche AH (1969) A review of aortic valve homografts over a six and one-half year period. *Ann Surg* 170:483–492. <https://doi.org/10.1097/0000658-19690910-00016>
- Boethig D, Goerler H, Westhoff-Bleck M, Ono M, Daiber A, Haverich A, Breyman T (2007) Evaluation of 188 consecutive homografts implanted in pulmonary position after 20 years. *Eur J Cardiothorac Surg* 32:133–142. <https://doi.org/10.1016/j.ejcts.2007.02.025>
- Burkert J, Kochová P, Tonar Z, Cimrman R, Blassová T, Jashari R, Fiala R, Špatenka J (2021) The time has come to extend the expiration limit of cryopreserved allograft heart valves. *Cell Tissue Bank* 22(2):161–184. <https://doi.org/10.1007/s10561-020-09843-2>
- Chambers J, Sandoe J, Ray S, Prendergast B, Taggart D, Westaby S, Arden C, Grothier L, Wilson J, Campbell B, Gohlke-Bärwolf C, Mestres CA, Rosenhek R, Pibarot P, Otto C (2014) The infective endocarditis team: recommendations from an international working group.

- Heart 100:524–527. <https://doi.org/10.1136/heartjnl-2013-304354>
- David TE, Gavra G, Feindel CM, Regesta T, Armstrong S, Maganti MD (2007) Surgical treatment of active infective endocarditis: a continued challenge. *J Thorac Cardiovasc Surg* 133:144–149. <https://doi.org/10.1016/j.jtcvs.2006.08.060>
- Dekens E, Van Damme E, Jashari R, Van Hoeck B, François K, Bové T (2019) Durability of pulmonary homografts for reconstruction of the right ventricular outflow tract: how relevant are donor-related factors? *Interact Cardiovasc Thorac Surg* 28:503–509. <https://doi.org/10.1093/icvts/ivy316>
- European directorate for the quality of medicines & health-care of the council of Europe (2019) Guide to the quality and safety of tissues and cells for human application. EDQM, 4th edn. Council of Europe, Strasbourg https://www.europarl.europa.eu/EPRS/Guide_to_the_quality_and_safety_of_tissues_and_cells_for_human_application.pdf
- Fukushima S, Tesar PJ, Pearse B, Jalali H, Sparks L, Fraser JF, Pohlner PG (2014) Long-term clinical outcomes after aortic valve replacement using cryopreserved aortic allograft. *J Thorac Cardiovasc Surg* 148:65–72.e2. <https://doi.org/10.1016/j.jtcvs.2013.07.038>
- Golemovic M, Skific M, Haluzan D, Pavic P, Golubic Cepulic B (2022) Ten-year experience with cryopreserved vascular allografts in the croatian cardiovascular tissue Bank. *Cell Tissue Bank* 7:1–18. <https://doi.org/10.1007/s10561-022-09992-6>
- Grosse K, Meyer R, Schmitzer E, Hetzer R, Wesslau C (2008) Are heart valves from donors over 65 years of age morphologically suitable for transplantation? *Cell Tissue Banking* 9:31–36. <https://doi.org/10.1007/s10561-007-9052-1>
- Habib G, Lancellotti P, Antunes MJ, Bongiorno MG, Casalta JP, Del Zotti F, Dulgheru R, El Khoury G, Erba PA, Iung B, Miro JM, Mulder BJ, Plonska-Gosciniak E, Price S, Roos-Hesselink J, Snygg-Martin U, Thuny F, Tornos Mas P, Vilacosta I, Zamorano JL (2015) 2015 ESC guidelines for the management of infective endocarditis: the task force for the management of infective endocarditis of the European society of cardiology (ESC). Endorsed by: European association for cardio-thoracic surgery (eacts), the European association of nuclear medicine (EANM). *Eur Heart J* 36(44):3075–3128
- Hopkins RA (1989) Historical development of the use of homograft valves In: cardiac reconstructions with allograft valves. Springer, New York 3–13 https://doi.org/10.1007/978-1-4612-3568-2_1
- Jashari R (2021) Transplantation of cryopreserved human heart valves in Europe: 30 years of banking in Brussels and future perspectives. *Cell Tissue Bank* 22(4):519–537. <https://doi.org/10.1007/s10561-021-09902-2>
- Jashari R, Goffin Y, Van Hoeck B, Vanderkelen A, du Verger A, Fan Y, Holovska V, Fagu A, Brahy O (2010) Belgian and European experience with the European homograft bank (EHB) cryopreserved allograft valves assessment of a 20 year activity. *Acta Chir Belg* 110(3280):290. <https://doi.org/10.1080/00015458.2010.11680618>
- Musci M, Hübler M, Amiri A, Stein J, Kosky S, Meyer R, Weng Y, Hetzer R (2010a) Surgical treatment for active infective prosthetic valve endocarditis: 22-year single-center experience. *Eur J Cardiothorac Surg* 38(5):528–538. <https://doi.org/10.1016/j.ejcts.2010.03.019>
- Musci M, Weng Y, Hübler M, Amiri A, Pasic M, Kosky S, Stein J, Siniawski H, Hetzer R (2010b) Homograft aortic root replacement in native or prosthetic active infective endocarditis: twenty-year single-center experience. *J Thorac Cardiovasc Surg* 139:665–673. <https://doi.org/10.1016/j.jtcvs.2009.07.026>
- Nappi F, Nenna A, Petitti T, Spadaccio C, Gambardella I, Lusini M, Chello M, Acar C (2018) Long-term outcome of cryopreserved allograft for aortic valve replacement. *J Thorac Cardiovasc Surg* 156:1357–1365. <https://doi.org/10.1016/j.jtcvs.2018.04.040>
- Nappi F, Avtaar Singh SS, Timofeeva I (2020) Learning from controversy: contemporary surgical management of aortic valve endocarditis. *Clin Med Insights Cardio* 14:1179546820960729. <https://doi.org/10.1177/1179546820960729>
- O'Brien MF, Stafford EG, Gardner MA, Pohlner PG, McGiffin DC (1987) A comparison of aortic valve replacement with viable cryopreserved and fresh allograft valves, with a note on chromosomal studies. *J Thorac Cardiovasc Surg* 94:812–823
- Pettersson GB, Hussain ST (2019) Current AATS guidelines on surgical treatment of infective endocarditis. *Ann Cardiothorac Surg* 8(6):630–644. <https://doi.org/10.21037/acs.2019.10.05>
- Poinot N, Fils JF, Demanet H, Dessy H, Biarent D, Wauthy P (2018) Pulmonary valve replacement after right ventricular outflow tract reconstruction with homograft vs Contegra®: a case control comparison of mortality and morbidity. *J Cardiothorac Surg* 13(1):8. <https://doi.org/10.1186/s13019-018-0698-5>
- Rodefeld MD, Ruzmetov M, Turrentine MW, Brown JW (2008) Reoperative right ventricular outflow tract conduit reconstruction: risk analyses at follow up. *J Heart Valve Dis* 17(1):119–126
- Ross DN (1962) Homograft replacement of the aortic valve. *Lancet* 2:487
- Russo M, Taramasso M, Guidotti A, Pozzoli A, Nietilspach F, Von Segesser L, Maisano F (2017) Lessons can be learned from the history of heart valve prostheses. The evolution of surgical valves. *Cardiovasc Med* 20(12):285–292. <https://doi.org/10.4414/cvm.2017.00532>
- Tweddell JS, Pelech AN, Frommelt PC, Mussatto KA, Wyman JD, Fedderly RT, Berger S, Frommelt MA, Lewis DA, Friedberg DZ, Thomas JP Jr, Sachdeva R, Litwin SB (2000) Factors affecting longevity of homograft valves used in right ventricular outflow tract reconstruction for congenital heart disease. *Circulation* 102(130):135. https://doi.org/10.1161/circ.102.suppl_3.III-130
- Willets RG, Stickley J, Drury NE, Mehta C, Stumper O, Khan NE, Jones TJ, Barron DJ, Brawn WJ, Botha P (2021) Four right ventricle to pulmonary artery conduit types. *J Thorac Cardiovasc Surg* 162(5):1324–1333.e3. <https://doi.org/10.1016/j.jtcvs.2020.12.144>

Yankah AC, Klose H, Petzina R, Musci M, Siniawski H, Hetzer R (2002) Surgical management of acute aortic root endocarditis with viable homograft: 13-year experience. *Eur J Cardiothorac Surg* 21:260–267. [https://doi.org/10.1016/s1010-7940\(01\)01084-3](https://doi.org/10.1016/s1010-7940(01)01084-3)

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