Durable circulatory support with a paracorporeal device as an option for pediatric and adult heart failure patients

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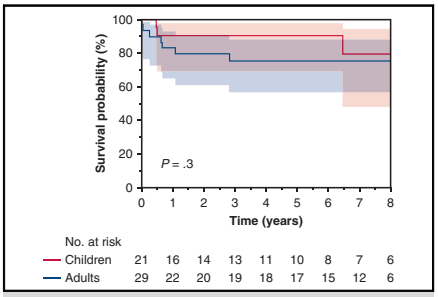
ABSTRACT

Objectives: Not all patients in need of durable mechanical circulatory support are suitable for a continuous-flow left ventricular assist device. We describe patient populations who were treated with the paracorporeal EXCOR, including children with small body sizes, adolescents with complex congenital heart diseases, and adults with biventricular failure.

Methods: Information on clinical data, echocardiography, invasive hemodynamic measurements, and surgical procedures were collected retrospectively. Differences between various groups were compared.

Results: Between 2008 and 2018, a total of 50 patients (21 children and 29 adults) received an EXCOR as bridge to heart transplantation or myocardial recovery. The majority of patients had heart failure compatible with Interagency Registry for Mechanically Assisted Circulatory Support profile 1. At year 5, the overall survival probability for children was 90%, and for adults 75% ($P = .3$). After we pooled data from children and adults, the survival probability between patients supported by a biventricular assist device was similar to those treated with a left ventricular assist device/ right ventricular assist device (94% vs 75%, respectively, $P = .2$). Patients with dilated cardiomyopathy had a trend toward better survival than those with other heart failure etiologies (92% vs 70%, $P = .05$) and a greater survival free from stroke (92% vs 64%, $P = .01$). Pump house exchange was performed in nine patients due to chamber thrombosis (n = 7) and partial membrane rupture (n = 2). There were 14 cases of stroke in eleven patients.

Conclusions: Despite severe illness, patient survival on EXCOR was high, and the long-term overall survival probability following heart transplantation and recovery was advantageous. Treatment safety was satisfactory, although still hampered by thromboembolism, mechanical problems, and infections. (J Thorac Cardiovasc Surg 2021;161:1453-64)



Overall survival probability in children and adults.

CENTRAL MESSAGE

Use of the paracorporeal EXCOR device as bridge to transplantation or recovery in children and adults less suitable for a CF-LVAD may offer good long-time outcomes with satisfactory safety.

PERSPECTIVE

Not all patients in need for a long-term MCS are suitable for a CF-LVAD, including children with small body sizes, patients with complex congenital heart diseases, and those with biventricular heart failure requiring right-sided support. In such cases treatment with the EXCOR system appears to be a viable strategy offering good results, although still hampered with a certain risk for complications.

See Commentaries on pages 1465, 1466, and 1467.

Today, the continuous-flow (CF) left ventricular assist device (LVAD) is the primary durable mechanical circulatory support (MCS) system applied for patients with left ventricular (LV) heart failure (HF) awaiting transplantation or recovery.[1] Still, not all patients in need of a long-term MCS are suitable for a CF-LVAD.[2-4] Such patients may include infants and children with small body sizes, adolescents and adults with complex congenital heart diseases, and patients with biventricular failure requiring additional right-sided support. Although,

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Abbreviations and Acronyms

BiVAD = biventricular assist device
BTT = bridge to transplantation
CF = continuous flow
DCM = dilated cardiomyopathy
ECMO = extracorporeal membrane oxygenation
HF = heart failure
HTx = heart transplantation
INTERMACS = Interagency Registry for Mechanically Assisted Circulatory Support
LV = left ventricular
LVAD = left ventricular assist device
MCS = mechanical circulatory support
RV = right ventricular/ventricle
RVAD = right ventricular assist device

Scanning this QR code will take you to the table of contents to access supplementary information.

short-term extracorporeal life support can be life-saving in these situations, the prolonged use of such systems is associated with significant morbidity and mortality[5,6] and has a negative effect on posttransplant outcomes.[7-10]

The Berlin Heart EXCOR system (Berlin Heart, GmbH, Berlin Germany) is a paracorporeal, pneumatically driven blood pump that delivers a pulsatile flow and can provide durable support of the LV, the RV, or both ventricles.[11] The device is available in a wide range of sizes that are developed to support both children and adults and is applicable for patient populations who are not suitable for CF-LVADs.[6,12] In Europe, the system is approved for both children and adults, but in the United States, its use is only granted for children.[13] As compared with CF-LVAD, the extracorporeal EXCOR device inflicts a greater intrusion on quality of life and results in greater complication rates. This influences its application as a bridge to transplantation and precludes its use as destination therapy.

At our institution, the EXCOR system has been used in children as a bridge to transplant (BTT) or recovery since 2008 and in adults as a BTT since 2010. The aim of this study was to describe patients receiving EXCOR pumps, their preimplantation profiles, outcomes, and pump-related complications. Apart from comparing the outcomes of children versus adults, we also studied the results for various subgroups to explore the effect of EXCOR treatment in different patient populations.

PATIENTS AND METHODS

Patient Demographics

Between April 2008 and December 2018, a total of 50 patients (21 children and 29 adults) received an EXCOR device (Berlin Heart GmbH) at Sahlgrenska University Hospital. All patients were included in the present analysis. In children, the strategy with long-term MCS could be either BTT or myocardial recovery, whereas all adults received the device as BTT.

At our pediatric department, the EXCOR device has been used as the primary system for long-term MCS in infants and children, mainly due to the scarcity of other durable alternatives. Thus, for children with small body sizes, the EXCOR was considered the only option for bridge to heart transplantation (HTx) or recovery. Notably, 3 older children with larger body sizes received an HVAD, but they are not included in the present analysis.

In adolescents and adults, we have used the system in selected patients considered ineligible for CF-LVAD, including those with complex congenital heart disease in whom intracorporeal device placement can be challenging and in patients in need for biventricular support.

After experiencing inferior results following LVAD implantation in critically ill adults with poor RV function, we adapted a more liberal use of planned in advance biventricular assist device (BiVAD). The decision to apply a BiVAD as treatment strategy was based on the estimated risk for postimplant RV failure after a multidisciplinary evaluation of clinical, echocardiographic, and hemodynamic status.

Blood samples were analyzed at the Central Laboratory of Sahlgrenska University Hospital (accredited according to European norm 45001). The study protocol was approved by the central ethical review board at the University of Gothenburg (Registration number 728-12).

Echocardiography

All patients were examined preoperatively according to standard transthoracic echocardiography protocols for children and adults, respectively. RV dysfunction and tricuspid valve regurgitation were graded as none (0), mild (1), moderate (2), or severe (3). Tricuspid annular plane systolic excursion and tissue Doppler velocity imaging of the RV free wall were measured in adults only due to differences in the examination protocols.

Invasive Hemodynamic Measurements

Invasive hemodynamic data from right heart catheterizations were obtained in all adults and in the majority of children. These measurements were performed as part of heart failure workup before decision-making on EXCOR treatment. In patients compatible with Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profile 1, who were admitted acutely and required extracorporeal membrane oxygenation (ECMO) support, the hemodynamic profile was acquired in the intensive care unit. Central venous pressure, right atrial pressure, mean pulmonary artery pressure, and pulmonary capillary wedge pressure were measured with a Swan–Ganz catheter, and cardiac output was determined by the Fick method in children and the thermodilution technique in adults. Pulmonary vascular resistance was calculated as the pressure difference between mean pulmonary artery pressure and pulmonary capillary wedge pressure divided by cardiac output and expressed as Wood units.

Surgical Procedure

The surgical introduction of the EXCOR pump was performed in a standard fashion using sternotomy and extracorporeal circulation in both children and adults. In most of the children, cannulas were implanted after induction of ventricular fibrillation. This was found to be practical by the pediatric surgeons, who have gained significant experience performing short procedures during ventricular fibrillation. This method facilitated emptying air from the ventricle and did not in any way affect RV function. Cardioplegia was used in 4 children and in 1 child the cannula was inserted

on a beating heart. For systemic ventricle support, the LV apex was cannulated in 15 patients, the RV in one, and both ventricles were supported in 5. In 4 children the left atrium was cannulated due to restrictive LV physiology, in 2 for anatomical considerations (1 child with congenitally corrected transposition of the great arteries and 1 child with myocarditis to facilitate device explantation). Seven of the children were supported with ECMO before durable EXCOR therapy was applied, and 2 had received cardiopulmonary resuscitation before implantation of the short-term MCS.

In adults receiving EXCOR as a BiVAD, implantation of cannulas was performed on a beating heart. Cannulas according to size of patients were inserted in the following sequence of order: left ventricular apex; right atrium; pulmonary artery; and aorta. Each cannula was carried through the skin in a similar fashion, ensuring appropriate distance between exit sites.

Both children and adults were weaned from extracorporeal circulation without inotropic support by connecting the EXCOR cannulas to short-term MCS devices (CentriMag [Abbott, Pleasanton, Calif] for children and Rotaflow PLS system [Maquet, Rastatt, Germany] for adults). After initial recovery, when patients were extubated and found to be neurologically intact, an exchange from the short-term MCS devices to the EXCOR pump houses was performed in a separate short procedure before leaving the intensive care unit.

Postoperative Management and Follow-up

Heparin infusion was initiated when bleeding had ceased postoperatively (24-48 hours) and activated partial thromboplastin time was targeted at 40 to 50 seconds. Warfarin treatment was started after the removal of chest tubes with international normalized ratio (INR) targeted at 2.5 to 3.5. Patients also received aspirin at a dose of 75 mg daily. In a few cases, where frequent thrombus formation in the pump houses had occurred, clopidogrel 75 mg was added after consulting a coagulation specialist. With respect to blood pressure control we aimed at levels $\leq$130/80 mm Hg. After stabilization, the patients were transferred to the cardiology ward, where they received physiotherapy and self-care training. Patients who remained clinically stable and had adequate social support were discharged to home with the "Excor mobile driving unit."

After HTx or weaning involving explantation of the EXCOR device, all patients were followed up at an outpatient clinic dedicated for HTx or HF, respectively. Within the frame of the study, we registered the occurrence of death and stroke (major and minor) during a maximum period of 8 years following EXCOR treatment.

Statistics

Statistical analyses were performed with JMP 10 and SAS 9.4 statistical software (SAS Institute, Cary, NC). Data are presented as means and standard deviations, medians and interquartile ranges, or numbers and percentages. Comparisons between children and adults were performed for all variables, despite self-evident disparities, to underline the differences between these 2 groups. Still, since many variables were similar between children and adults, we allowed us to pool data from the 2 groups to increase the power for other statistical analyses. Statistical comparisons between children and adults both at baseline and during follow-up were performed with an unpaired t test for normally distributed data, Mann–Whitney U test for nonparametric data and Fisher exact test for categorical data.

Cumulative incidence of HTx or weaning during the first year was estimated with competing risks regression models according to the model by Fine–Gray.[14] In these analyses, deaths were treated as competing events. Comparison of the following subgroups were performed: children versus adults; male versus female; LVAD/right ventricular assist device (RVAD) treatment versus BiVAD treatment; dilated cardiomyopathy (DCM) HF etiology versus other HF etiologies; and INTERMACS = 1 versus INTERMACS >1.

Curves for overall survival and for survival free from major stroke were completed. In the latter analysis, we comprised a combined end point, including time to stroke or time to death, whichever came first, and censored alive patients without stroke with a cut off after a maximum of 8 years. Kaplan–Meier curves were generated for children versus adults; male versus female; LVAD/RVAD treatment versus BiVAD treatment; DCM HF etiology versus other HF etiologies; and INTERMACS = 1 versus INTERMACS >1. Since time to death was applied as an end point and not as a competing event, the use of the competing risk in these analyses is inadequate and comparison between the groups was achieved with the Wilcoxon test.

RESULTS

Patient Characteristics

During the study period, participants were treated with the EXCOR system for a total of 5990 days. Among children for 2062 days and among adults for 3928 days. Demographics, medical history, and preoperative laboratory values are shown in Table 1. The distribution of sex was similar for both pediatric and adult study groups. More children had undergone previous cardiac surgery as compared with adults, but heart failure duration was shorter for children than for adults. In all of the children and in 97% of the adults the heart failure etiology was nonischemic.

Table 2 displays preoperative echocardiography data; hemodynamic status; need for circulatory, ventilatory or renal support; and clinical heart failure severity (INTERMACS profiles). Echocardiography showed similar LV ejection fraction in both children and adults. Severe impairment of RV function was more common in adults, reflecting the selection of the EXCOR system as a BiVAD treatment. The presence of 2 or more of the risk factors for postoperative RV failure listed in Table E1 favored BiVAD implantation. Invasive hemodynamic measurements displayed high filling pressures and low flow with severely reduced mixed venous saturation in both groups. The use of intravenous inotropic support was high in both children and adults. Treatment with various types of short-term MCS devices was common in both study groups, and ECMO was used in 7 children (47%) and in 9 adults (34%). The majority of patients were compatible with INTERMACS profile 1, with no differences between children and adults. The different types of congenital heart disease in patients treated with EXCOR are displayed in Table E2. Separate consort diagrams for children and adults showing the use of all types of long-term MCS support at our center during the study period are provided in Figures E1 and E2.

Treatment Strategy, Hospital Stay, and Time on Assist

Table 3 presents treatment strategy, hospital stay, and time on assist in children and adults, respectively. The device was used as an LVAD in 15 children, as an RVAD in one child, and as a BiVAD in 5 children. The child, who received the device as an RVAD, had a univentricular heart

TABLE 1. Demographics, medical history, and preoperative laboratory values in pediatric and adult patients

	Pediatric patients (n = 21)	Adult patients (n = 29)	*P* value
Demographics			
Age, y	5 (1-11)	35 (23-48)	<.001
Female sex	10 (48)	12 (41)	.7
Body mass index, kg/m^2	16 ± 2	25 ± 4	<.001
Body surface area, m^2	0.79 ± 0.48	1.96 ± 0.27	<.001
Medical history			
Hypertension	1 (5)	0 (0)	.2
Diabetes	0 (0)	1 (3)	.4
Atrial fibrillation/flutter	2 (10)	6 (21)	.3
Myocardial infarction	0 (0)	2 (7)	.2
Previous cardiac surgery	14 (67)	7 (24)	.003
Duration of heart failure, mo	0.5 (0.1-1)	6 (1-66)	.006
Etiology of heart failure			
Dilated cardiomyopathy	9 (43)	17 (59)	.3
Congenital heart disease	6 (29)	2 (7)	.04
Myocarditis/inflammatory heart disease	2 (10)	4 (14)	.6
Postoperative/procedural complications	0 (0)	3 (10)	.1
Ischemic heart disease	0 (0)	1 (3)	.4
Graft failure post–heart transplantation	1 (5)	0 (0)	.2
Other	3 (14)	2 (7)	.4
Laboratory values			
Hemoglobin, g/L	112 ± 25	120 ± 19	.2
Creatinine, μmol/L	43 ± 28	120 ± 50	<.001
Aspartate aminotransferase, μkat/L	1.3 (0.9-2.7)	0.7 (0.5-3.4)	.08
Alanine aminotransferase, μkat/L	1.3 (0.4-1.7)	0.8 (0.4-1.7)	.6
Bilirubin, μmol/L	12 (6-15)	20 (14-33)	<.001

Values are presented as means ± standard deviation, numbers (%), or medians (interquartile range).

defect consisting of hypoplastic left heart syndrome and had undergone Norwood and a subsequent bidirectional Glenn procedure. The child had the device implanted in the morphological RV, which supported the systemic circulation.

One child with congenitally corrected transposition had the morphologic RV as the systemic ventricle and had the device for support of the systemic circulation with cannulas implanted in the left atrium and aorta. In the adult population, the system was used as an LVAD in 1 patient, and as a BiVAD in 25 subjects. The adult patient, who received the device as an LVAD had a history of transposition of the great arteries, Senning correction, Rashkind septostomy, and recent ICD-lead endocarditis. The patient was converted from ECMO to short-term LVAD connected through the Excor cannulas, and later on equipped with an EXCOR pump house.

At the beginning of our program, we had a restrictive attitude toward discharging patients with paracorporeal devices. After our experience with the system increased, we became aware that it was feasible to discharge patients to their home. One child aged 10 years of age and 13 adults were discharged to home on device during the wait time ($P = .002$). These patients were followed closely at a cardiac daycare facility with trained staff. Family members and home nurses were also trained to perform daily inspections of the pump houses and regular check-up of the system. In cases where the patients lived in another region of the country, members of our team trained the staff at the local hospital. The longest treatment on pump was 344 days, of which the patient spent 30 days at home. The patient with the longest time of home support had a total time on device of 327 days, of which he spent 255 days at home. The most common out of hospital complication included wound infections around the cannulas, which in some cases required hospitalization and treatment with intravenous antibiotics. In general, patients discharged to home tended to do better than those who remained hospitalized (data not shown).

HTx and Weaning

HTx was performed in 12 children (57%) and 24 adults (83%) ($P = .05$). Myocardial recovery allowing for explantation occurred in 8 children (38%) and 1 adult (3%) ($P < .001$). The heart failure etiologies associated with myocardial recovery in children included tachycardia-induced cardiomyopathy (n = 2), DCM (n = 1), myocarditis (n = 2), congenital aortic stenosis

TABLE 2. Preoperative clinical heart failure severity and hemodynamic status and circulatory, ventilatory, and renal support

	Children (n = 21)	Adults (n = 29)	*P* value
Echocardiographic measurements			
Left ventricular ejection fraction, %	23 ± 8	19 ± 8	.2
Severe RV failure	3 (15)	24 (83)	<.001
TVR grade, 0-3	1.7 ± 1.0	1.9 ± 0.8	.6
TAPSE, cm	ND	1.3 ± 0.3	ND
RV free wall peak tissue velocity, cm/s	ND	7.0 ± 2.1	ND
Invasive hemodynamic measurements			
Heart rate, beats/min	129 ± 18	104 ± 27	.06
Right atrial pressure, mm Hg	12 ± 4	14 ± 5	.4
Mean pulmonary artery pressure, mm Hg	37 ± 14	31 ± 15	.4
Pulmonary capillary wedge pressure, mm Hg	23 ± 8	20 ± 5	.3
Systolic blood pressure, mm Hg	83 ± 15	92 ± 10	.03
Cardiac index, L/min/m^2	2.7 ± 0.5	1.5 ± 0.5	.001
SvO_2, %	56 ± 5	52 ± 11	.5
Circulatory, ventilatory and renal support			
Intravenous inotropic therapy	18 (86)	25 (86)	.9
Short-term mechanical circulatory support*	11 (73)	19 (73)	.9
Mechanical ventilation	13 (62)	13 (45)	.2
Continuous renal-replacement therapy	2 (10)	7 (26)	.2
Clinical heart failure severity			
INTERMACS profile 1 (vs 2-5)	9 (60)	16 (62)	.9

Values are presented as means ± standard deviation or n (%). *RV*, Right ventricular; *TVR*, tricuspid valve regurgitation; *TAPSE*, tricuspid annular plane systolic excursion; *ND*, not done; *SvO_2*, mixed venous saturation; *INTERMACS*, Interagency Registry for Mechanically Assisted Circulatory Support. *Short-term (ST) mechanical circulatory support involved different combinations of intra-aortic balloon pump, extracorporeal membrane oxygenation; ST-left ventricular assist device, or ST-biventricular assist device

(n = 1), and anomalous left coronary artery from the pulmonary artery (n = 2). The adult patient that was weaned from the EXCOR system had suffered from a perioperative myocardial infarction. Seven children who underwent explantation after 31, 46, 73, 77, 79, 84, and 110 days (6 LVADs and 1 BiVAD) survived without recurrent heart failure or need for heart transplantation. However, one child, who underwent LVAD explantation after 59 days, developed restrictive myocardial physiology and died of cardiogenic shock three months later. The adult patient, who underwent BiVAD explantation after 79 days, had developed a stroke and was not any longer considered a transplant candidate despite compromised cardiac function, and died of neurologic sequalae 5 months later.

One child (5%) died on pump due to severe gastrointestinal bleedings and multiple organ failure at day 180. In the adult group, 4 patients died on pump (14%): 1 of multiple organ failure at day 17, 1 due to a stroke at day 32, 1 due to stroke at day 97 (following multiple infectious complications), and 1 following a major cerebral bleed at day 245.

TABLE 3. Treatment strategy, hospital stay, time on assist, and outcome

	Children (n = 21)	Adults (n = 29)	*P* value
Type of assist			
LVAD	15 (71)	1 (3)	<.001
RVAD (supporting the systemic circulation)	1 (5)	0 (0)	.4
BiVAD	5 (24)	28 (97)	<.001
Hospital stay, time on assist, discharge			
Length of stay in ICU, d	15 (11-29)	18 (7-30)	.9
Length of stay in hospital, d	79 (39-111)	66 (43-100)	.6
Time on assist, d	79 (39-239)	136 (81-185)	.08
Discharge to home on device	1 (5)	13 (45)	.002
HTx and recovery			
Heart transplantation	12 (57)	24 (83)	.05
Recovery	8 (38)	1 (3)	.002
Death on device	1 (5)	4 (14)	.3

Values are presented as numbers (%) or median (interquartile range). *LVAD*, Left ventricular assist device; *RVAD*, right ventricular assist device; *BiVAD*, biventricular assist device; *ICU*, intensive care unit; *HTX*, heart transplantation.

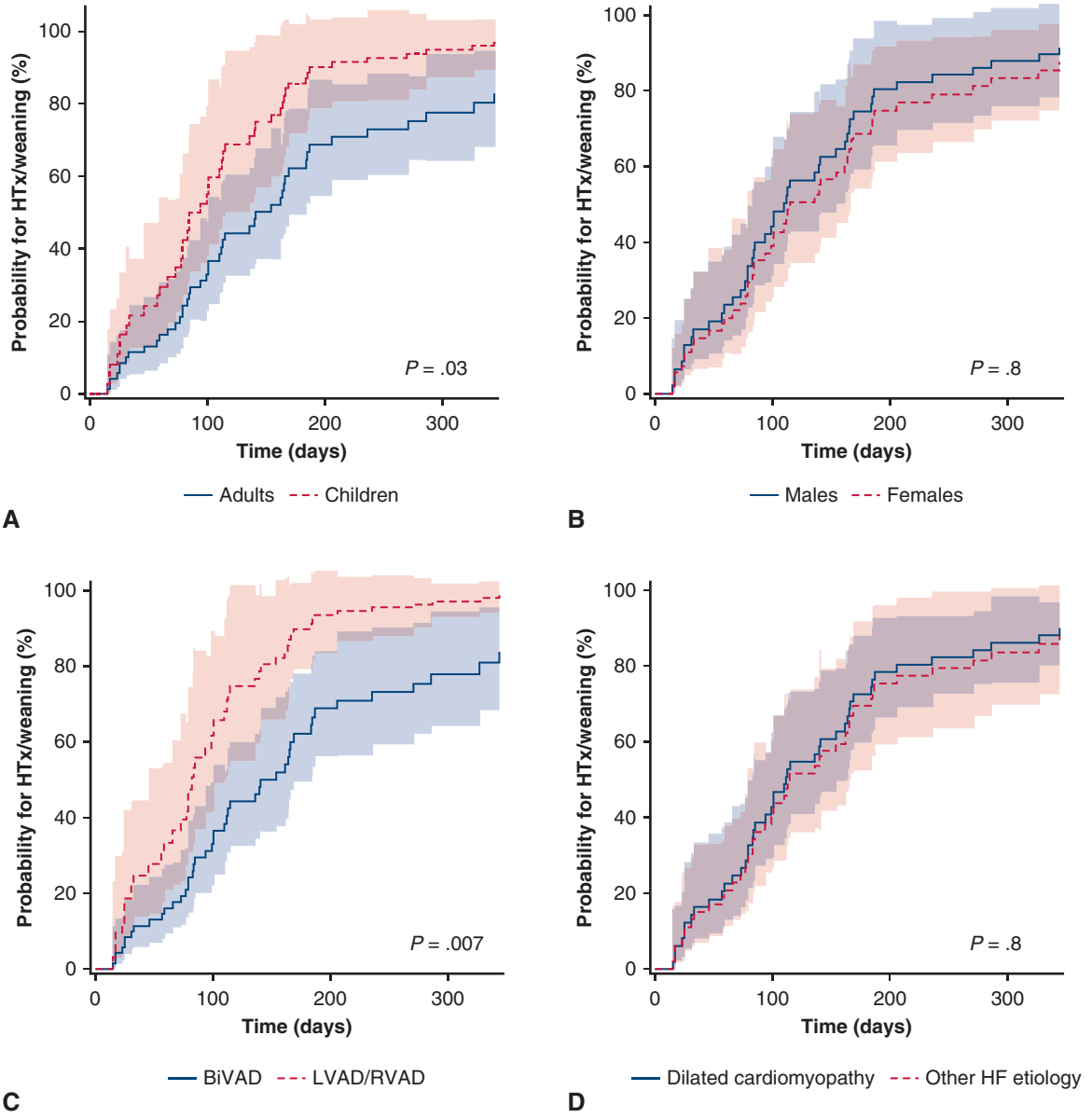


FIGURE 1. Time on EXCOR device to HTx (n = 36) or weaning (n = 9) during the first year of follow-up in different subgroups. A, Children versus adults; B, males versus females; C, treatment with BiVAD versus LVAD/RVAD; and D, DCM versus other heart failure etiology. Cumulative incidence of HTx or weaning during the first year was estimated with competing risks regression models, in which deaths were treated as competing events. *HTx*, Heart transplantation; *BiVAD*, biventricular assist device; *LVAD*, left ventricular assist device; *RVAD*, right ventricular assist device; *HF*, heart failure.

Short-Term Survival and Wait Times on Device

The proportion of the total study population surviving on device until heart transplantation or weaning was 90%. All survivors were transplanted or weaned from the pump within 1 year of follow-up (Figure 1). No patient was considered for destination therapy. Children were listed for HTx directly after pump-implantation. Time to transplantation or weaning was shorter for children (85 days; interquartile range 46-165 days), than for adults (125 days; interquartile range 76-186 days) ($P = .03$), who were listed first after a 3-month rehabilitation period (Figure 1, *A*). When data from children and adults were pooled, there was no significant difference between females and males with respect to time to HTx/weaning (Figure 1, *B*). The patients who received an LVAD or RVAD, were mainly children and had a shorter wait time to HTx/weaning than those who were treated with a BiVAD, largely adults ($P = .007$) (Figure 1, *C*). There was no difference in wait time between those who had DCM compared with those that with other HF etiologies

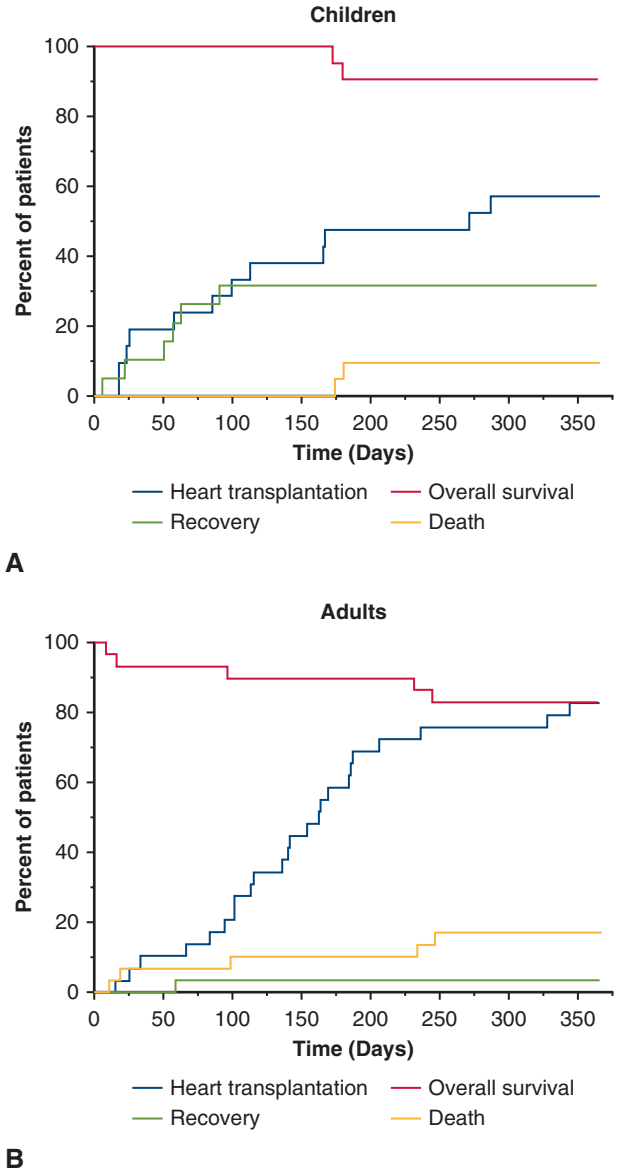


FIGURE 2. Outcomes for children and adults after implantation of the EXCOR device. A, All outcomes over time for children during 12 months of follow-up after EXCOR implantation. B, All outcomes over time for adults during 12 months of follow-up after EXCOR implantation.

(Figure 1, *D*). Patients compatible with INTERMACS profile 1 had similar wait times to HTx and recovery as those with INTERMACS levels 2 or greater (Figure E3, *A*). Figure 2 depicts competing outcomes with respect to survival, cumulative HTx, recovery, and mortality in children (Figure 2, *A*) and in adults (Figure 2, *B*), respectively.

Adverse Events Related to EXCOR Treatment

Thirty-day postoperative complications and pump-related complications are shown in Table 4. Complications within 1 month after device introduction included reoperations due to bleeding, need for continuous renal-replacement therapy, mediastinitis, pneumonia, and different types of hospital-acquired bacteremia. These complications did not differ between children and adults. Among pump-related complications, during the entire time of support, there were 14 cases of stroke in 11 patients. In 6 patients (5 adults and 1 child) the strokes were major (defined as considerable residual neurologic symptoms). Five of six major strokes were primarily ischemic and one was hemorrhagic. In 3 of these cases, the strokes were directly linked to the patients' death. The 6 patients with minor strokes had no or very discrete residual neurologic symptoms. One child had a subarachnoid hemorrhage but showed no residual symptoms at the time of discharge.

The potential development of fibrin depositions, red clots, or white thrombus on the inflow or outflow valves was followed with close surveillance. If this occurred, our first response was to optimize the anticoagulation. If international normalized ratio was below 2.5 we added low molecular heparin subcutaneously and adjusted the warfarin dose. If antithrombin III was low (<0.8 KIE/L) this was given intravenously in an adequate dose. In some cases, we added clopidogrel 75 mg after consulting a coagulation specialist. Pump chamber thrombosis requiring intervention occurred in 5 children and four adults, and in most cases pump chamber exchange was performed in the operation theater. In selected cases, the pediatric thoracic surgeons dismantled the pump house and if easily accessible removed red clots and thrombi after which they rinsed the pump house with saline. Subsequently, the pump house was reattached to the cannulas. In adults we attempted to optimize the anticoagulation regime for a longer period of time before performing any interventions.

Two cases of membrane rupture among adults were solved by urgent pump chamber exchange. Cannula infection requiring antibiotics occurred in 5 children and 7 adults. Bleeding complications were uncommon. One child suffered from a major gastrointestinal bleeding that was eventually fatal. After HTx or weaning, we only registered death and stroke as adverse events.

Long-Term Survival During and After EXCOR Treatment

Overall survival probability and survival free from major stroke through a maximal follow-up of 8 years during and after EXCOR treatment is depicted in Figure 3, Figure E3, *B* and *C*, and Figure E4. Note that "survival free from major stroke" is a combined end point, including time to stroke or time to death, whichever came first. During a median follow-up of 5.4 years (interquartile range 2.6-7.7 years) the survival probability for children at 1 and 5 years was 90% and 90%, respectively. The corresponding survival probability for adults was 82% and 75%, respectively (Figure 3, *A*). When data from

TABLE 4. Summary of adverse events: postoperative complications up to 30 days after pump implantation and all pump-related complications during EXCOR treatment

	Children (n = 21)		Adults (n = 29)		*P* value
Postoperative complications					
Reoperation due to bleeding	7 (33)		10 (34)		.9
Continuous renal-replacement therapy	2 (10)		3 (10)		.8
Mediastinitis (ABX-treated)	0 (0)		3 (10)		.1
Pneumonia (ABX-treated)	1 (5)		5 (17)		.2
Hospital-acquired bacteremia (ABX-treated)	2 (10)		6 (21)		.3
	n (%)	**Events/pat yr.**	**n (%)**	**Events/pat yr.**	
Pump-related complications					
Major stroke	1 (5)	0.18	5 (17)	0.46	.2
Minor stroke	4 (19)	0.71	5 (17)	0.46	.9
Pump thrombosis requiring intervention	5 (24)	0.88	4 (14)	0.37	.4
Mechanical pump failure	0 (0)	0.00	2 (7)	0.19	.2
Cannula infection treated with ABX	5 (24)	0.88	7 (27)	0.65	.9

Values are presented as numbers (%) and events per patient years. *ABX*, Antibiotics.

children and adults were pooled, there was no difference in survival probability between those treated with a BiVAD and those in whom one ventricle was supported (LVAD/RVAD) (Figure 3, *C*). With respect to survival free from stroke the time to event appeared earlier, but since cerebral strokes were the main cause of death in children vs adults, and in those with BiVAD vs LVAD/RVAD, long-term survival was largely unchanged (Figure 3, *B* and *D*). In a similar manner, there were no differences between female and male patients (Figure E4, *A* and *B*). Patients who had DCM as heart failure etiology had a strong trend toward better overall survival (96% at year 1 and 92% at year 5) compared with those with other HF etiologies (75% at year 1 and 70% at year 5) ($P = .05$). Survival free from major stroke was significantly greater in patients with DCM compared with those with other HF etiologies (92% vs 64% after 5 years, $P = .01$) (Figure E4, *C* and *D*). Patients compatible with INTERMACS profile 1 had a similar long-term outcome as those with INTERMACS levels 2 or higher (Figure E3, *B* and *C*).

DISCUSSION

The present study supports the usefulness of the paracorporeal EXCOR-system as BTT or recovery in both children and adults with advanced heart failure who are less suitable for CF-LVADs. Considering the severity of their illness, survival on device and long-term survival probability following HTx or recovery was high and better than previously reported.[6,15-18] The safety of the system was acceptable, although the treatment is still hampered by complications including thromboembolism, mechanical problems, and infections.

Most implantable MCS are developed to support a failing LV causing inadequate circulation in adult patients. Although there has occurred a certain miniaturization along with the transition from pulsatory to continuous flow techniques, there is still the issue of a device–body size mismatch in children. The remaining alternatives for these patients have been nonpulsatile ECMO and centrifugal pumps, which demand continuous care in the intensive care unit, resulting in immobilization, increased risk for infections, thromboembolic events, and poor outcome.[6,8-10] For longer-term support, the only realistic option for infants and small children has been the paracorporeal EXCOR pump.[6,15] The 21 children treated with the EXCOR system in our study could be transferred to the general ward and one child was discharged to home during the wait time for HTx. The children displayed an excellent survival on the EXCOR pump to HTx or recovery, followed by a high long-term survival probability.

Advances in neonatal care consisting of improved detection and repair of complex cardiac lesions has led to a growing population of adolescents and adults with complex congenital heart disease. These patients have an increased risk for heart failure and have a high mortality risk.[19] Therefore, this patient population constitutes an increasing need for a durable MCS as bridge to heart transplantation. However, the implantation of a CF-LVAD in these cases can be problematic due to anatomic variations that may render device placement difficult. Further, data on the treatment of patients suffering from congenital heart disease with durable MCS are scarce. In the present study a total of 6 patients (4 children and 2 adults) with complex congenital heart disease received an EXCOR system as bridge to HTx or recovery. Four patients (3 children and 1 adult) underwent HTx; in 1 child myocardial function recovered permitting explantation of the device; and 1 adult died on device. The 1- and 5-year survival probability for

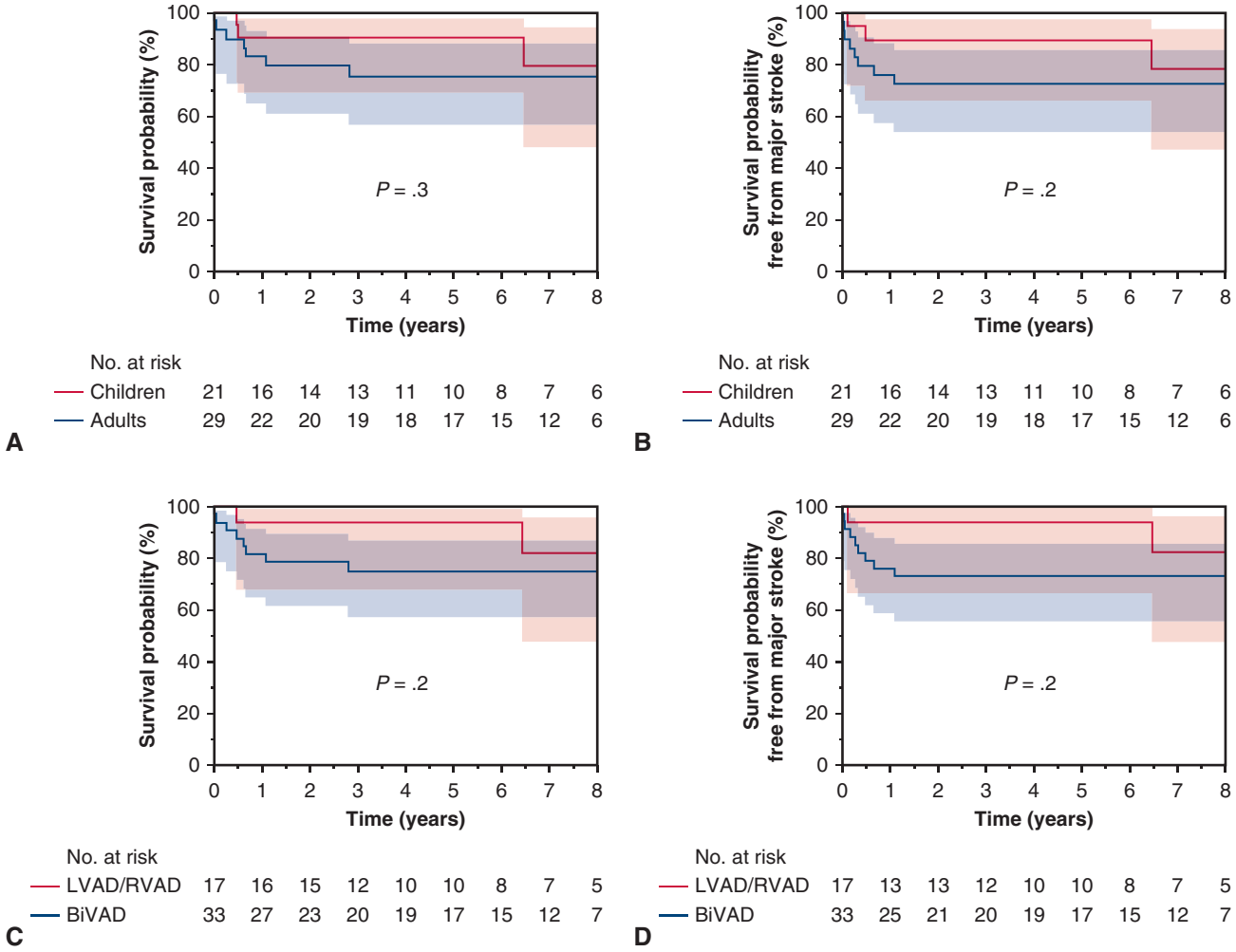


FIGURE 3. Overall survival probability and survival free from stroke for patients throughout and after EXCOR treatment during 8 years of follow-up. Overall survival in: A, children versus adults; B, survival free from disabling stroke in children versus adults; C, overall survival in patients receiving BiVAD versus LVAD/RVAD; and D, overall survival in patients with DCM vs other heart failure etiology. *LVAD*, Left ventricular assist device; *RVAD*, right ventricular assist device; *BiVAD*, biventricular assist device.

these patients were 83% at both time points, which is high, considering the anatomical complexity of their cardiac malformations and the severity of their illness.

The treatment of severe biventricular HF with MCS is controversial. Early right HF develops in approximately 20% to 30% of all LVAD recipients and is associated with a substantial increase in mortality.[20-22] The management of this problem with a subsequent short-term right-sided assist or durable CF-RVAD during the wait for HTx or recovery is associated with a less-favorable outcome, often with 1-year survival in the range of 50% to 70% or less.[23,24] In previous systematic evaluations using older paracorporeal systems, treatment has also consistently shown worse outcomes.[25-27] In contrast, there are data suggesting that preplanned BiVAD implantation in patients with a high risk of RV failure is better than subsequent conversion from LVAD to BiVAD.[28] In a previous study, we observed that patients with high risk of postimplant RV failure experienced excellent survival rates when subjected to a planned in advance BiVAD strategy using the paracorporeal EXCOR system.[29] The outcomes for these patients were similar to that observed for contemporary LVAD recipients. These findings are confirmed in the present study in which patients with biventricular failure displayed a high survival on device to HTx and a good long-term survival probability. During the recent years, we have observed that patients are referred for HTx workup earlier in their disease course, and prior to the development of severe right ventricular failure. This, along with the development of miniature, but powerful intracorporal CF LVADs, may diminish the need for BiVAD implantation in the future.

Due to its versatility as a circulatory support system, our findings suggest that the EXCOR pump is a valuable option

in patients ineligible for CF-LVAD.[30] The EXCOR device offers a longer circulatory support, allowing for improved nutrition status, mobilization with optimization of fitness, and recovery of organ dysfunction and a better outcome than bridging with short-term MCS. Children were listed for HTx directly after EXCOR implantation, whereas adults were admitted to a 3-month rehabilitation program before HTx listing for optimization in order to minimize operative risks. This approach may result in loss of adult patients on pump, but outweighs, in our opinion, the risk of organ waste associated with death following a high-risk transplantation. Thus, we believe that the strategy of optimizing adults for three months before HTx listing is adequate and can improve long-term survival in this severely ill population.

In the present study, a total of 42% of patients were discharged to home during wait time for HTx, which is likely to reduce operative risks. At our center, average wait times are short, which probably, in part, limits the risk for development of long-term complications and contributes to a good long-term outcome. The longest time on pump was 344 days and the longest time on pump at home was 255 days. Due to patient discomfort and an increased risk for complications, a pulsatile BiVAD is not suitable for an extended period of treatment. Therefore, if EXCOR became available for adults in the United States, we would propose that patients on this device should receive a higher priority than those treated with a CF-LVAD.

As expected, there were several differences between children and adults with respect to EXCOR treatment. More children had congenital heart disease, and they had lower creatinine due to lower muscle mass. Cardiac index was greater in children, which is a known phenomenon.[31] A majority of children received the EXCOR as an LVAD, whereas in adults the pump-system was almost exclusively implanted as a BiVAD, which illustrates the versatility of the device. A significantly greater proportion of adults were discharged with the device. Further, the rate of myocardial recovery was much higher in children. Our findings suggest that the likelihood of myocardial recovery is related to age, disease duration and heart failure etiology. Patients of younger age with short disease duration and reversible causes of heart failure, such as myocardial inflammation or tachyarrhythmia, are more likely to embrace a potential for reverse remodeling. Among the eight children who experienced recovery of myocardial function allowing for pump explantation, 7 had either tachycardia-induced-cardiomyopathy, myocarditis or persistent severe heart failure after a surgical procedure. These diagnoses were less common among children who did not recover, although no statistical differences between groups could be shown due to small numbers. The 2 children with myocarditis were first treated with short-term MCS, but did not recover within a reasonable time period. Therefore, the treatment was converted to EXCOR-LVAD, which could be successfully explanted later on. In contrast, adults with long-term disease duration who do not respond to conventional pharmaceutical or resynchronization therapy are unlikely to show myocardial recovery allowing for explantation. Long-term survival was slightly greater in children than in adults, but this was not statistically significant. The wait time for HTx was significantly shorter for children, which can be explained by the practice to accept children for the wait list directly after pump-implantation, where adults are normally not admitted to the waitlist until they have performed our 3-month rehabilitation program.

In line with previous reports,[6,32] a significant number of patients were affected by procedure or device related adverse events during the present study. Early complications included bleeding, need for continuous renal-replacement therapy, mediastinitis and pneumonia, with similar frequencies in children and adults. Pump-thrombosis requiring intervention occurred in 24% of children and 14% of adults. This was managed mostly with pump change, but in some children the thrombus was removed following dismantling of the pump, which after rinsing was re-attached again. Although the relatively high frequency of stroke is a clear drawback related to EXCOR treatment, only a small proportion of this adverse event led to permanent sequelae (1 child and 5 adults). In contrast, a major stroke frequently led to death later on. In the present study patients with DCM had a significantly greater survival free from major stroke compared with those with other heart failure diagnoses. This probably reflects a more complicated course in those with congenital heart disease or other more complex cardiac disorders. Although the occurrence of cannula infection was significant, this problem could be solved with oral or intravenous antibiotics.

Limitations

The observational, retrospective nature of the study is an important limitation with respect to the type of evidence we can provide. Also, the moderate sample size and differences between adults and children constrain our conclusions. Patients with more complex congenital heart disease ($n = 6$) were too few to able us to draw strong conclusions about this group. We did not use uniform criteria to select the treatment strategy of LVAD or BIVAD; instead the decision was made on a multidisciplinary conference based on the estimated risk for postimplant RV failure. Although there were evident differences between children and adults, there were also several similarities, which allowed us to pool the 2 groups for certain statistical analyses. We acknowledge that EXCOR use has been previously described in pediatric populations. However, much less information about the use of the system in adults is available

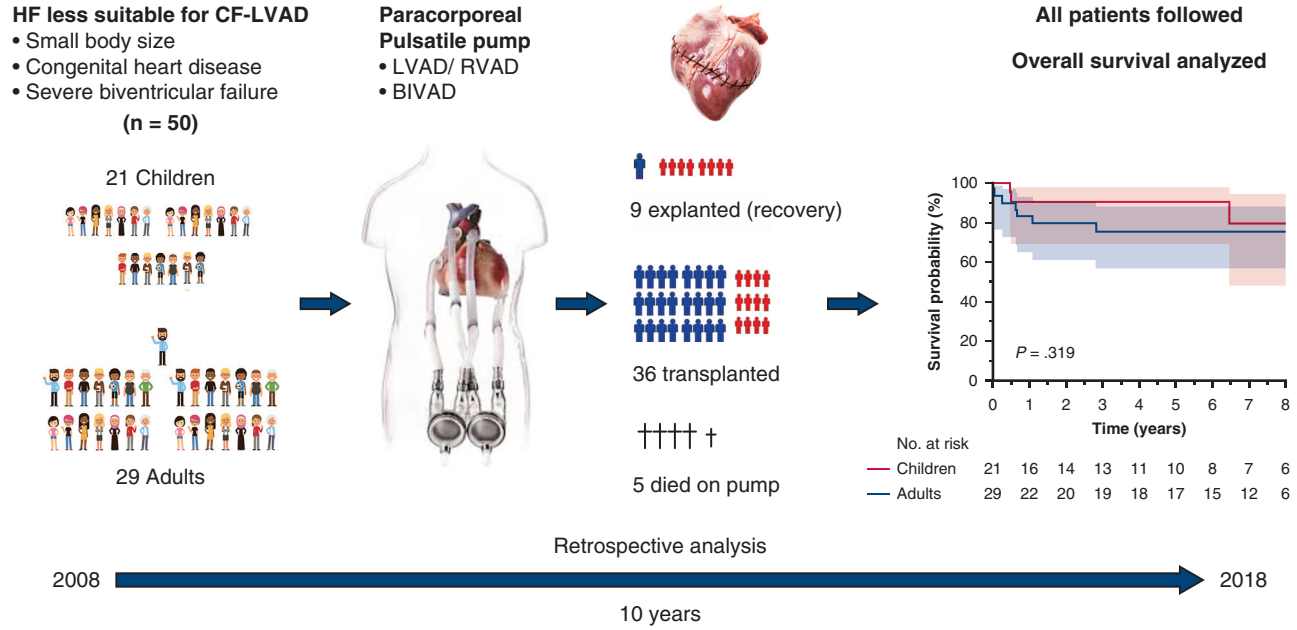
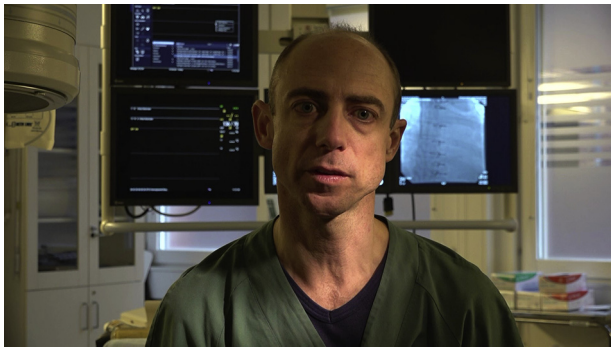


FIGURE 4. Graphical presentation of the study outline, study population, and outcome. *HF*, Heart failure; *CF*, continuous flow; *LVAD*, left ventricular assist device; *RVAD*, right ventricular assist device; *BiVAD*, biventricular assist device.

and the novelty of our study lies mainly in the application of the system in adults.

CONCLUSIONS

Not all patients in need for a long-term MCS are suitable for a CF-LVAD, including infants and children with small body sizes, adolescents and adults with complex congenital heart diseases, and patients with biventricular failure requiring additional right-sided support. Considering the severity of patient illness and disease complexity in many of our cases, the use of the paracorporal EXCOR as a bridge to transplantation or recovery resulted in a high survival. In addition, the overall long-term survival after HTx or recovery was remarkably good. Still, EXCOR treatment is hampered by complications including thrombo-embolism, mechanical problems and infections, requiring high surveillance and intensive clinical monitoring (Figure 4, Video 1).



VIDEO 1. The first author presenting a short abstract of the study, highlighting its background, aims, methods, and conclusions. Video available at: https://www.jtcvs.org/article/S0022-5223(20)31166-1/fulltext.

Conflict of Interest Statement

Dr Dellgren: Astellas Pharma Europe for an investigator-initiated study in immunosuppression after lung transplantation (the ScanCLAD study, ClinicalTrials.gov Identifier: NCT02936505); and Abbott regarding a destination therapy study on LVAD (the SweVAD study, Investigator initiated, ClinicalTrials.gov Identifier: NCT02592499). All other authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: mechanical circulatory support, left ventricular assist device (LVAD), biventricular assist device (BiVAD), Berlin Heart EXCOR system, continuous flow, pulsatile flow

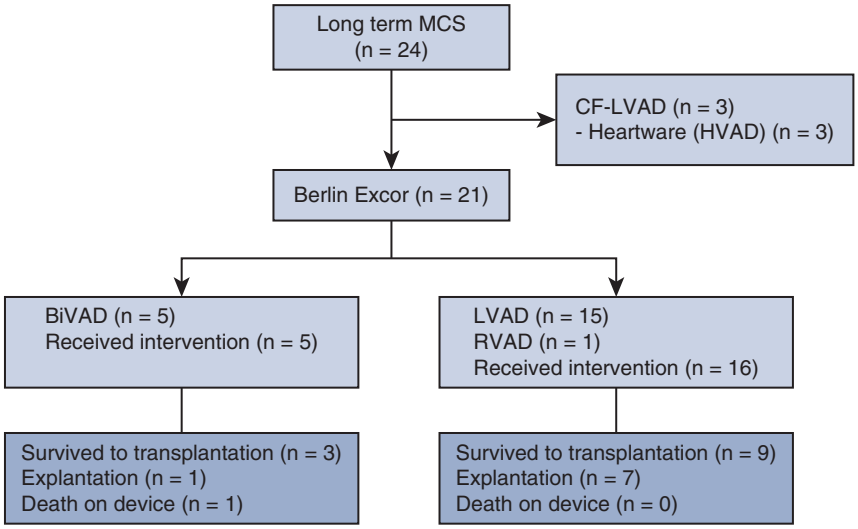

FIGURE E1. Flow diagram of children who received long-term MCS at Sahlgrenska University Hospital during the study period. *MCS*, Mechanical circulatory support; *CF*, continuous flow; *LVAD*, left ventricular assist device; *HVAD*, Heartware ventricular assist device; *BiVAD*, biventricular assist device; *RVAD*, right ventricular assist device.

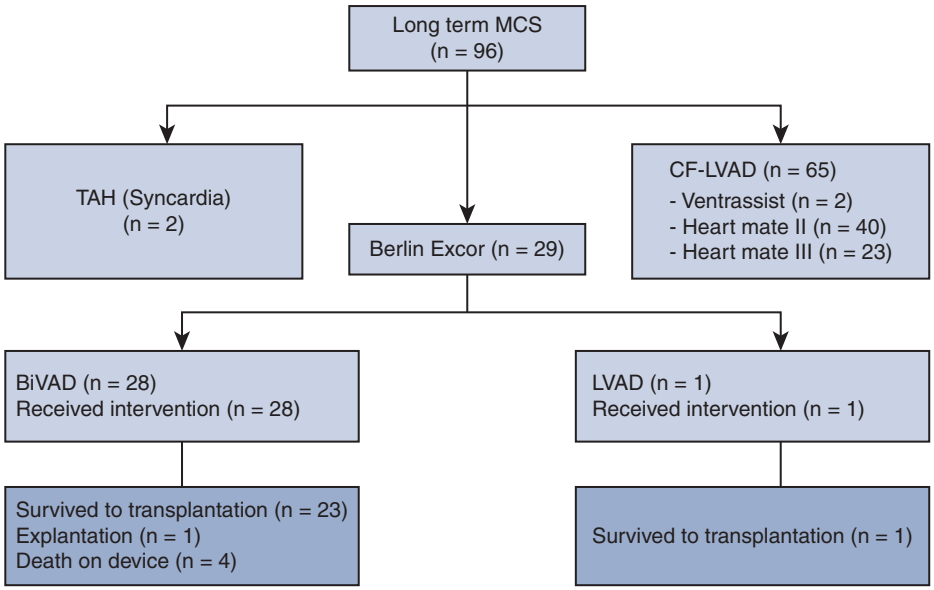

FIGURE E2. Flow diagram of adults who received long-term MCS at Sahlgrenska University Hospital during the study period. *MCS*, Mechanical circulatory support; *TAH*, total artificial heart; *CF*, continuous flow; *LVAD*, left ventricular assist device; *BiVAD*, biventricular assist device.

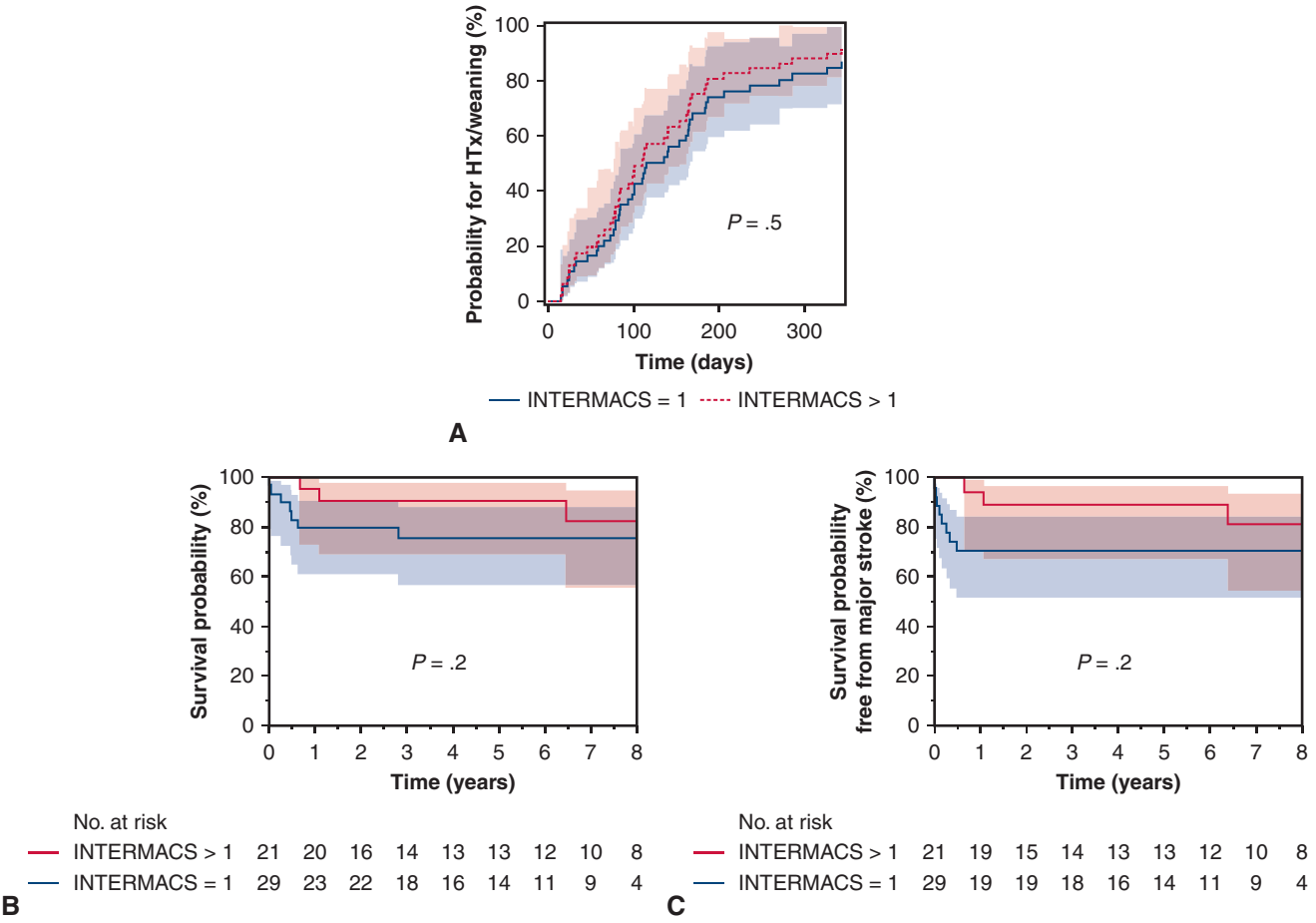

FIGURE E3. Time on EXCOR device and survival for patient with different INTERMACS profiles. A, Time on EXCOR to HTx or weaning for patients in INTERMACS = 1 versus those in INTERMACS >1. B, Overall survival in patients in INTERMACS = 1 versus those in INTERMACS >1. C, Survival free from disabling stroke in patients in INTERMACS = 1 versus those in INTERMACS >1. *HTx*, Heart transplantation; *INTERMACS*, Interagency Registry for Mechanically Assisted Circulatory Support.

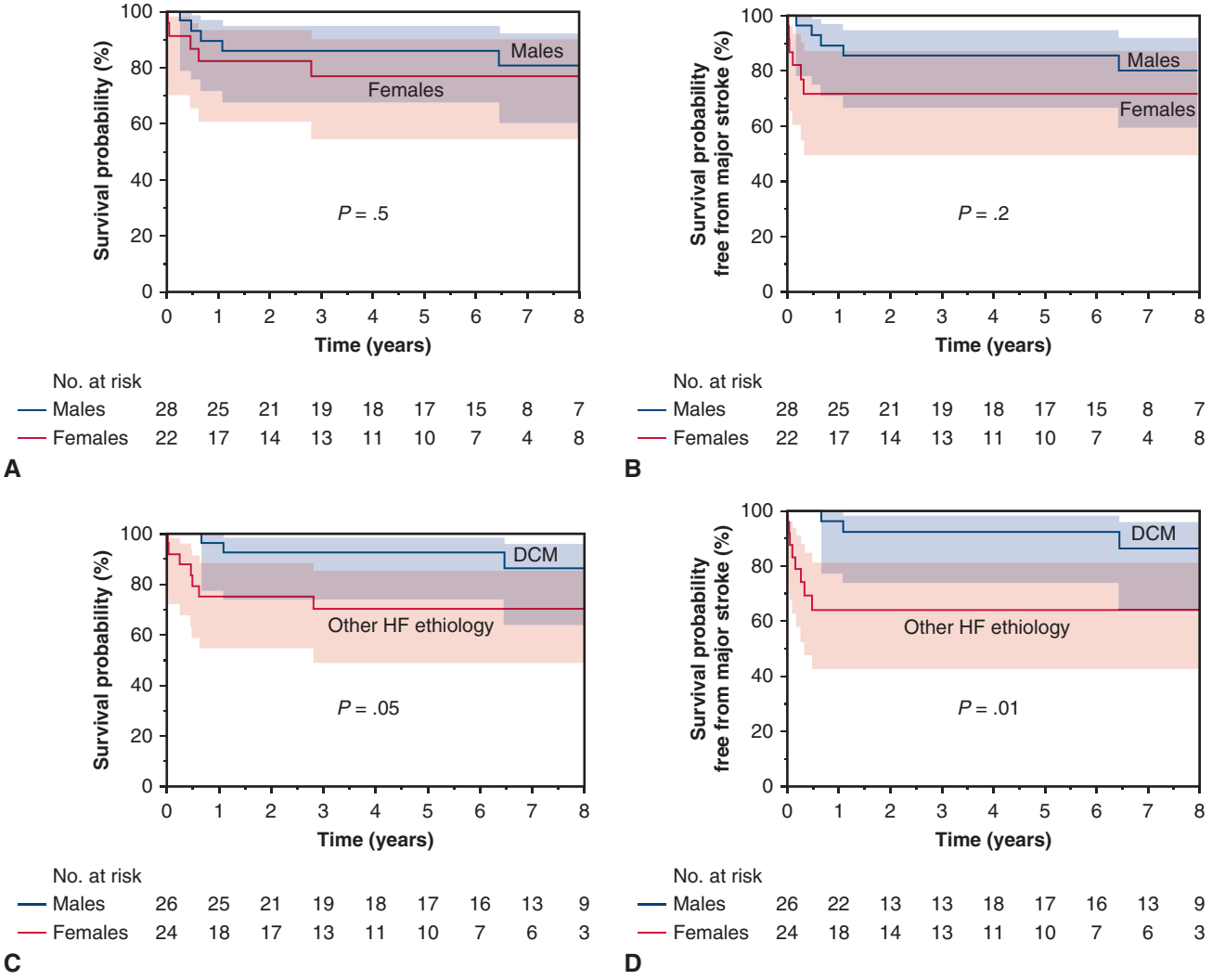

FIGURE E4. Overall survival probability and survival free from stroke for patients throughout and after EXCOR treatment during 8 years of follow-up. A, Overall survival in male versus female patients; B, survival free from disabling stroke in male versus female patients; C, overall survival in patients with DCM versus other HF etiology; and D, overall survival in patients with DCM versus other heart failure etiology. *DCM*, Dilated cardiomyopathy; *HF*, heart failure.

TABLE E1. Risk factors for postoperative right ventricular failure (the presence of 2 or more risk factors favored BiVAD implantation)

1	TAPSE <0.72 cm
2	RVEDD/LVEDD >0.72
3	CVP >16 mm Hg
4	MPAP–RAP <10 mm Hg (or SPAP-DPAP/CVP <0.5)
5	CVP/PCWP >0.63
6	RVSWI <300 mm Hg × mL/m^2
7	Bilirubin >34 μmol/L

TAPSE, tricuspid annular plane systolic excursion; *RVEDD*, right ventricular end-diastolic diameter; *LVEDD*, left ventricular end-diastolic diameter; *CVP*, central venous pressure; *MPAP*, mean pulmonary arterial pressure; *RPAP*, right pulmonary artery pressure; *SPAP*, systolic pulmonary artery pressure; *DPAP*, diastolic pulmonary artery pressure; *PCWP*, pulmonary capillary wedge pressure; *RVSWI*, right ventricular stroke work index.

TABLE E2. Patients with congenital heart diseases who received an EXCOR device in the present study

Patient	Age	Diagnosis	Type of VAD
1	Adult	Senning op (transposition)	Univentricular
2	Adult	Congenital aortic stenosis, LV elastosis, severe PH	Biventricular
3	Pediatric	HLHS, Norwood surgery + Glenn VAD to morphologic RV	Univentricular
4	Pediatric	Congenital aortic stenosis, LV elastosis	Univentricular
5	Pediatric	Congenital aortic vitium. Several surgical procedures, severe LV failure	Univentricular
6	Pediatric	cc-TGA, VAD to morphologic RV	Univentricular
7	Pediatric	ALCAPA. Severe LV failure postoperatively	Univentricular
8	Pediatric	ALCAPA. Severe LV failure postoperatively	Univentricular

VAD, Ventricular assist device; *LV*, left ventricular; *PH*, pulmonary hypertension; *HLHS*, hypoplastic left heart syndrome; *RV*, right ventricular; *cc-TGA*, congenitally corrected transposition of the great arteries; *ALCAPA*, anomalous left coronary artery from the pulmonary artery.