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REPORT

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The European Registry for Patients with Mechanical Circulatory Support (EUROMACS): second EUROMACS Paediatric (Paedi-EUROMACS) report

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Abstract

OBJECTIVES: A second paediatric report has been generated from the European Registry for Patients with Mechanical Circulatory Support (EUROMACS). The purpose of EUROMACS, which is operated by the European Association for Cardio-Thoracic Surgery, is to gather data related to durable mechanical circulatory support for scientific purposes and to publish reports with respect to the course of mechanical circulatory support therapy. Since the first report issued, efforts to increase compliance and participation have been extended. Additionally, the data provided the opportunity to analyse patients of younger age and lower weight.

METHODS: Participating hospitals contributed pre-, peri- and long-term postoperative data on mechanical circulatory support implants to the registry. Data for all implants in paediatric patients (≤19 years of age) performed from 1 January 2000 to 1 July 2019 were analysed. This report includes updates of patient characteristics, implant frequency, outcome (including mortality rates, transplants and recovery rates) as well as adverse events including neurological dysfunction, device malfunction, major infection and bleeding.

RESULTS: Twenty-nine hospitals contributed 398 registered implants in 353 patients (150 female, 203 male) to the registry. The most frequent aetiology of heart failure was any form of cardiomyopathy (61%), followed by congenital heart disease and myocarditis (16.4% and 16.1%, respectively). Competing outcomes analysis revealed that a total of 80% survived to transplant or recovery or are ongoing; at the 2-year follow-up examination, 20% died while on support. At 12 months, 46.7% received transplants, 8.7% were weaned from their device and 18.5% died. The 3-month adverse events rate was 1.69 per patient-year for device malfunction including pump exchange, 0.48 for major bleeding, 0.64 for major infection and 0.78 for neurological events.

CONCLUSIONS: The overall survival rate was 81.5% at 12 months following ventricular assist device implant. The comparison of survival rates of the early and later eras shows no significant difference. A focus on specific subgroups showed that survival was less in patients of younger age (<1 year of age) ($P = 0.01$) and lower weight (<20 kg) ($P = 0.015$). Transplant rates at 6 months continue to be low (33.2%) The fact that the EUROMACS registry is embedded within the European Association for Cardio-Thoracic Surgery Quality Improvement Programme offers opportunities to focus on improving outcomes.

†The first two authors contributed equally to this study.

Keywords: Mechanical circulatory support • Ventricular assist device • Paediatric patients • Registry • End-stage heart failure • Congenital heart disease

ABBREVIATIONS

BiVAD	Biventricular assist device
BSA	Body surface area
CI	Confidence interval
EUROMACS	European Registry for Patients with Mechanical Circulatory Support
HR	Hazard ratio
INTERMACS	Interagency Registry for Mechanically Assisted Circulatory Support
LVAD	Left ventricular assist device
MCS	Mechanical circulatory support
Pedimacs	Paediatric Interagency Registry for Mechanical Circulatory Support
VAD	Ventricular assist device

INTRODUCTION

The quantity of data for paediatric patients who suffer from end-stage heart failure treated with mechanical circulatory support (MCS) continues to grow. Because the number of patients implanted with a ventricular assist device (VAD) per centre remains relatively limited, the European Registry for Patients with Mechanical Circulatory Support (EUROMACS) provides a platform to collect data from multiple centres across Europe [1]. Within its Quality Improvement Programme, the European Association for Cardio-Thoracic Surgery provides the structure for the collection and registration of both paediatric and adult data of patients who receive MCS. A paediatric subcommittee of EUROMACS was installed to advise with respect to the evaluation of paediatric clinical data on adding specific data to increase the understanding of the course of MCS therapy in children and to assist in evaluating incoming paediatric study proposals.

EUROMACS collects data from children as well as adults who received a CE-marked durable assist device (Table 1). This approach enables the registry to not only select paediatric patients but also to follow them after they have passed the age of 19 years. Apart from heart transplant and death, weaning was also defined as a primary end point. To better understand and analyse the registry-based data on the clinical management and long-term outcomes in this patient population, follow-up is, as of 2019, continued after ventricle recovery.

Apart from the aim to provide professionals in the field of MCS with data for scientific research, the EUROMACS registry strives to generate benchmarking data for participants. Additionally, patient and device outcomes are structured in such a way that they are comparable with the Paediatric Interagency Registry for Mechanical Circulatory Support (Pedimacs) (2) and Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) outcomes (3).

As a result of the continuous contributions from the participating hospitals, this second paediatric report provides analysis of durable MCS until 1 July 2019. Now that the follow-up of paediatric patients after implantation provides data over a period of>8 years, longitudinal outcomes and comparisons between eras (≤2014 and ≥2015) have become possible.

Because an increasing number of patients are ongoing on durable VADs, this second EUROMACS paediatric report includes the data from the first report [1] and includes adverse events and end points after 31 December 2017.

METHODS

Since 1 January 2018, 6 additional hospitals joined EUROMACS. As of 1 July 2019, a total of 29 centres in 15 different countries (Table 2) submitted data to the EUROMACS registry on patients ≤19 years of age implanted with a VAD. The participating centres agreed to enter data of patients who consented (or their legal guardians, depending on local legislation in force). Newly enrolled centres were advised to submit data of patients who received MCS therapy since 1 January 2011. However, some centres that have contributed since the inception of EUROMACS have chosen to submit data from an earlier date, and 38 patients were registered before 1 January 2011.

Data quality checks and audits

The methods to ensure data reliability were mentioned in the first Paedi-EUROMACS Report [1]. In summary, these include statistical consistency and plausibility checks, on-site audits and feedback reports and update status per patient for each participant.

Statistical analyses

Baseline and follow-up data were reviewed as to completeness and chronology. Improbable records were corrected or eliminated after reconfirmation with on-site data managers of

Table 1: Mechanical circulatory support systems relevant to paediatric populations within EUROMACS

Durable devices	
Continuous flow	HeartAssist 5
	HeartMate II
	HeartWare HVAD
	HeartMate 3
	HeartWare MVAD
	Berlin Heart INCOR
Pulsatile	Thoratec PVAD
	Berlin Heart EXCOR
Total artificial heart	-
Short-term devices	Levitronix CentriMag

EUROMACS: European Registry for Patients with Mechanical Circulatory Support: HVAD: HeartWare ventricular assist device; MVAD: miniature ventricular assist device; PVAD: percutaneous ventricular assist device.

Table 2: Participating paediatric units providing data for this report

Country	City, hospital
Austria	• Innsbruck, Innsbruck University Clinics • Vienna, Medical University of Vienna
Belarus	• Minsk, Republican Scientific and Practical Center Cardiology
Belgium	• Gent, University Hospital Gent • Leuven, University Hospital Leuven
Czech Republic	• Brno, Center for Cardiovascular and Transplant Surgery • Prague, Institute for Clinical and Experimental Medicine
Germany	• Bad Oeynhausen, Herz und Diabeteszentrum Nordrhein-Westfalen • Berlin, Deutsches Herzzentrum Berlin • Freiburg, University Heart Center Freiburg Bad Krozingen
Hungary	• Budapest, Gottsegen Hungarian Institute of Cardiology
Italy	• Bergamo, Ospedale Papa Giovanni XIII • Bologna, San Orsola Hospital • Rome, Ospedale Pediatrico Bambino Gesù • Torino, Regina Margherita Children's Hospital
Kazakhstan	• Astana, National Research Cardiac Surgery Center
Netherlands	• Groningen, University Medical Center Groningen • Rotterdam, Erasmus University Medical Center • Utrecht, University Medical Center Utrecht
Poland	• Warsaw, Children's Memorial Hospital • Zabrze, Silesian Center for Heart Diseases
Slovakia	• Bratislava, Klinika Kardiochirurgie NUSCH
Spain	• La Paz University Hospital
Switzerland	• Bern, University Hospital Bern (Inselspital) • Zürich, Kinderspital Zürich
Turkey	• Ankara, Baskent University Hospital • Istanbul, Florence Nightingale University Hospital • Izmir, Ege University Hospital
UK	• London, Great Ormond Street Hospital

participating centres. Continuous variables are presented as mean ± standard deviation or median and range depending on distribution of data. For statistical analyses, the Student's *t*-test or Wilcoxon rank sum test was applied. Categorical variables are presented as number (*n*) and percentages of population. Analyses were performed with the χ^2 test or the Fisher's exact test as appropriate. A competing outcomes analysis was performed for a heart transplant, recovery/weaning, patients still on the device or death. Kaplan–Meier curves were generated for the complete group of patients supported by either a left VAD (LVAD) or a biventricular assist device (BiVAD). Patients for whom the device type was unknown were not included in any further analysis after the baseline data were submitted. Furthermore, Kaplan–Meier analyses were made for all patients, who were split into the following groups: LVAD versus BiVAD, age category, era (patients implanted ≤ 2014 or patients implanted ≥ 2015), device strategy, weight above or below 20 kg, body surface area (BSA) categories (<1, 1–1.5, >1.5 m^2), paracorporeal or intracorporeal LVAD, circulatory support before VAD implantation and aetiology of heart failure. Univariable and multivariable Cox regression analyses were performed for baseline predictors of death. Finally, all adverse events for the first 3 months and after 3 months were collected and calculated to determine events per patient-year. Adverse events, which included device malfunction, infection, neurological dysfunction and major bleeding, were captured according to INTERMACS Adverse Events definitions. Statistical analyses were performed with SPSS, version 25 (IBM Inc., Armonk, NY, USA) or R-studio [Core Team (2017), R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/] with the packages 'survival' and 'cmprsk'.

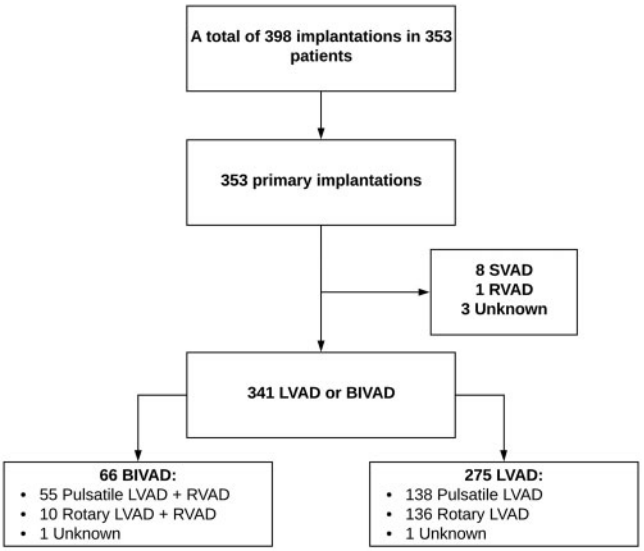

Figure 1: Flow chart. BiVAD: biventricular assist device; LVAD: left ventricular assist device; RVAD: right ventricular assist device; SVAD: systemic ventricular assist device.

RESULTS

Patient population

Between January 2000 and 1 July 2019, a total of 398 implants in 353 patients were registered (Fig. 1); 150 (42.5%) patients were female and 203 (57.5%) were male. The mean age was 8.9 years (±6.4 SD) and ranged from 0 to 19 years, with 55 (15.6%) patients below the age of 1 year. Baseline characteristics are specified in Table 3. Primary diagnoses on admission were cardiomyopathy in 215 (61%), myocarditis in 57 (16.1%), congenital heart disease in 58 (16.4%) and other in 23 (6.5%) (Table 3). VAD implantation was predominantly performed in patients with INTERMACS patient profiles 1, 2 and 3 (21.0%, 49.6% and 19.3%, respectively).

A total of 81.3% of the children were on inotropic support and 25.3% were on mechanical ventilation prior to VAD implantation. Extracardiac life support was used in 17.2%, whereas an intra-aortic balloon pump was used in 1.7% of the patients prior to VAD implantation. Thirty-nine patients received a second device after the first one; 5 patients received a third and 1 patient, a fourth implant (Table 4). A full specification of the types of devices used can be found in Table 5. Of all patients, 51.6% were supported by the Berlin Heart EXCOR® (Berlin Heart, Berlin, Germany), 4.8% by the HeartMate II® (Abbott, Chicago, IL, USA), 3.7% by the HeartMate 3 (Abbott, Chicago, IL, USA), 0.6% by HeartAssist5® (Micromed, Houston, TX, USA) and 31.7% by HeartWare HVAD® (Medtronic, Minneapolis, MN, USA). In 70 patients, 1 (or multiple) concomitant cardiac procedure(s) (12 congenital, 19 valve procedures and 47 other procedures) were performed. The breakdown and the specifications of the congenital heart defects are provided in Table 6. The majority of

Table 3: Baseline characteristics

	Overall	Era I (*n* = 156)	Era II (*n* = 197)	*P*-value
Age (years)				
Median (range)	10 (0–19)	9 (0.2–19)	10 (0–19)	0.674
Mean ± SD	8.9 ± 6.4	8.8 ± 6.7	9.1 (6.2)	
Sex, *n* (%)				0.279
Male	203 (57.5)	95 (60.9)	108 (54.8)	
Female	150 (42.5)	61 (39.1)	89 (45.2)	
Age categories (years), *n* (%)				0.121
1	55 (15.6)	31 (19.9)	24 (12.2)	
1–5	82 (23.2)	34 (21.8)	48 (24.4)	
6–10	53 (15.0)	18 (11.5)	35 (17.8)	
10	163 (46.2)	73 (46.8)	90 (45.7)	
Weight categories (kg), *n* (%)				0.424
<5	11 (3.2)	5 (3.3)	6 (3.0)	
5–20	139 (40.5)	63 (40.4)	76 (38.6)	
21–40	68 (19.8)	23 (14.7)	45 (22.8)	
41–60	62 (18.1)	31 (19.9)	31 (15.7)	
>60	63 (18.4)	28 (17.9)	35 (17.8)	
Unknown	10 (2.9)	6 (3.8)	4 (2.0)	
Body surface area (m^2)				
Median (range)	1.04 (0.18–2.53)	1.03 (0.21–2.09)	1.04 (0.18–2.53)	0.610
Mean ± SD	1.07 ± 0.58	1.05 ± 0.59	1.08 ± 0.57	
Body mass index (kg/m^2)				
Median (range)	15.8 (8.1–37.7)	15.9 (9.8–31.2)	15.7 (8.1–37.7)	0.489
Mean ± SD	17.0 ± 4.6	17.1 ± 4.4	17.0 ± 4.8	
Total bilirubin levels (mg/dl)				
Median (range)	1.06 (0.03–25.0)	1.00 (0.03–25.0)	1.20 (0.12–25.0)	0.104
Mean ± SD	1.97 ± 3.22	1.76 ± 3.12	2.14 ± 3.31	
Creatinine (mg/dl)				
Median (range)	0.67 (0.20–3.75)	0.67 (0.20–3.75)	0.69 (0.20–2.10)	0.932
Mean ± SD	0.76 ± 0.45	0.79 ± 0.55	0.74 ± 0.36	
eGFR (ml/min/1.73 m^2)				
Median (range)	82 (18–211)	83 (19–153)	82 (18–229)	0.218
Mean ± SD	86 ± 35	80 ± 30	88 ± 38	
Primary diagnosis, *n* (%)				0.097
Dilated cardiomyopathy	192 (54.4)	81 (51.9)	111 (56.3)	
Congenital heart disease	58 (16.4)	32 (20.5)	26 (13.2)	
Myocarditis	57 (16.1)	28 (17.9)	29 (14.7)	
Restrictive cardiomyopathy	19 (5.4)	10 (6.4)	9 (4.6)	
Hypertrophic cardiomyopathy	4 (1.2)	1 (0.6)	3 (1.5)	
Valvular heart disease	5 (1.4)	0 (0)	5 (2.5)	
Coronary artery disease	1 (0.3)	0 (0)	1 (0.5)	
Cancer	2 (0.6)	0 (0)	2 (1.0)	
Unknown	15 (4.2)	4 (2.6)	11 (5.6)	
INTERMACS patient profile, *n* (%)				0.671
INTERMACS 1	74 (21.0)	35 (22.4)	39 (19.8)	
INTERMACS 2	175 (49.6)	76 (48.7)	99 (50.3)	
INTERMACS 3	68 (19.3)	35 (22.4)	33 (16.8)	
INTERMACS 4	15 (4.2)	7 (4.5)	8 (4.1)	
INTERMACS 5–7	10 (2.8)	3 (1.9)	7 (3.6)	
Unknown	11 (3.1)	0 (0)	11 (5.6)	
Number of inotropes, *n* (%)				0.451
0	38 (10.8)	20 (12.8)	18 (9.1)	
1–2	180 (51.0)	76 (48.7)	104 (52.8)	
3–4	66 (18.7)	33 (21.1)	33 (16.8)	
≥5	3 (0.8)	2 (1.3)	1 (0.5)	
Unknown	66 (18.7)	25 (16.0)	41 (20.8)	
Mechanical ventilation, *n* (%)	87 (25.3)	33 (21.2)	54 (28.9)	0.033
Renal replacement therapy, *n* (%)	13 (3.8)	8 (5.1)	5 (2.7)	0.301
Circulatory support, *n* (%)				
IABP	6 (1.7)	3 (1.9)	3 (1.6)	1.000
ECLS	59 (17.2)	22 (14.1)	37 (19.8)	0.077
Device type, *n* (%)				<0.005
LVAD	275 (77.9)	115 (73.7)	160 (81.2)	
LVAD + temporary RVAD	12 (3.4)	2 (1.3)	10 (5.1)	
RVAD	1 (0.3)	1 (0.6)	0 (0)	
BiVAD	54 (15.3)	37 (23.7)	17 (8.6)	
SVAD	8 (2.3)	1 (0.6)	7 (3.6)	
Unknown	3 (0.8)	0 (0)	3 (1.5)	

Continued

Table 3: Continued

	Overall	Era I (n = 156)	Era II (n = 197)	P-value
Current device strategy, n (%)				0.476
Bridge to transplant	190 (53.8)	80 (51.3)	110 (55.8)	
Possible bridge to transplant	104 (29.5)	46 (29.5)	58 (29.4)	
Rescue therapy	28 (7.9)	15 (9.6)	13 (6.6)	
Bridge to recovery	27 (7.6)	15 (9.5)	12 (6.1)	
Unknown/other	4 (1.1)	0 (0)	4 (2.0)	

BiVAD: biventricular assist device; ECLS: extracorporeal life support; eGFR: estimated glomerular filtration rate; IABP: intra-aortic balloon pump; INTERMACS: Interagency Registry for Mechanically Assisted Circulatory Support; LVAD: left ventricular assist device; RVAD: right ventricular assist device; SD: standard deviation; SVAD: systemic ventricular assist device.

Table 4: Primary and subsequently implanted devices

Device	First	Second	Third	Fourth	Total
BiVAD	54	2	0	0	56
LVAD	275	20	2	0	297
LVAD, RVAD	12	1	0	0	13
RVAD	1	6	2	1	10
SVAD	8	1	0	0	9
Unknown	3	9	1	0	13
Total	353	39	5	1	398

BiVAD: biventricular assist device; LVAD: left ventricular assist device; RVAD: right ventricular assist device; SVAD: systemic ventricular assist device.

Table 5: Type of primary implanted ventricular assist device per age group

Device set-up	<1	1–5	6–10	>10	Total
LVAD alone					
Pulsatile	41	49	25	23	138
Continuous		6	18	112	136
Unspecified		1			1
LVAD, temporary RVAD					
Continuous LVAD, continuous RVAD				7	7
Pulsatile LVAD, continuous RVAD	2	2	1		5
BiVAD					
Pulsatile	8	16	6	20	50
Continuous		1	2		3
Unspecified		1			1
SVAD					
Pulsatile				2	2
Continuous		2		3	5
Unspecified				1	1
RVAD					
Unknown				1	1
Unknown		1	1	1	3

BiVAD: biventricular assist device; LVAD: left ventricular assist device; RVAD: right ventricular assist device; SVAD: systemic ventricular assist device.

Table 6: Congenital heart diseases (70 diagnoses in 59 patients)

Congenital heart disease	n
Complete atrioventricular septal defect	5
Transposition of the great arteries	8
Hypoplastic left heart	7
Single ventricle	4
VSD/ASD	14
Tetralogy of Fallot	1
ALCAPA	3
Ebstein's anomaly	1
Left heart structural/valvular	3
Other/unknown	24

ALCAPA: anomalous left coronary artery from the pulmonary artery; ASD: atrial septal defect; VSD: ventricular septal defect.

patients (83.3%) were treated with the intention to transplant (i.e. bridge to transplant or possible bridge to transplant); this was true across all age groups (Table 7).

Outcomes

The median support time on a device was 4.2 months (range 0–83.6 months). The median stay in the intensive care unit was 22 days (range 0–422 days). A total of 265 (80%) children survived to transplant or recovery or remain on MCS at the 2-year follow-up (Fig. 2). At 6 months, 33.2% of the patients and at the first year, 46.7% of the children received a transplant. This percentage increased to 57.5% at 2 years post VAD implantation. In the overall follow-up period, 68 patients died, 38.2% of whom died of cerebrovascular accidents. Thirteen patients (19.1%) died of multiorgan failure. The primary cause of death was not specified for 8 patients (Table 8).

Overall survival and subgroup analyses

Kaplan–Meier actuarial survival of all paediatric patients with MCS was 79.9% at 6 months, 75.5% at 12 months and 67.9% at 2 years, respectively, with censoring at time of explantation for transplant or for recovery (Supplementary Material, Fig. S1). When stratified for device type, LVAD or BiVAD, 81.3% survival was observed in the first year for LVADs and 52.9% for BiVADs ($P < 0.0001$) (Fig. 3).

When stratified by age, the oldest group (11–19 years) had an 84.5% survival rate at the end of the first year and 78.4% at the end of the second year; the age group 6–10 years had an 80.3% 1-year survival rate; the age group 1–5 years had a 69.4% survival rate at the end of the first year. Patients <1 year old had the poorest survival rate of 49.3% at 1 year ($P = 0.01$) (Fig. 4).

Supplementary Material, Figure S2 shows the survival analysis of all patients by era. Era 1 includes all patients who received implants before 2015; era 2 includes all patients who received implants as of 1 January 2015. The 2-year survival rate was 71.2% in era 1 and 65.4% in era 2 ($P = 0.92$). The 1-year survival rate stratified by device strategy reveals survival rates of 82% for bridge to recovery, 78.9% for bridge to transplant, 74.7% for possible bridge to transplant and the worst survival rate (51%) for rescue therapy ($P = 0.0019$) (Fig. 5). Figure 6 depicts the survival analysis of patients who weighed less than or more than 20 kg and reveals a significantly worse survival rate for patients weighing <20 kg ($P = 0.015$). Similarly, patients with a lower BSA (<1 m^2 or between 1 and 1.5 m^2) have a significantly worse survival rate than patients with a BSA of 1.5 m^2 or higher ($P = 0.0099$) (Fig. 7). Survival of patients supported by a paracorporeal device compared to patients supported by an intracorporeal device reveals a significantly worse survival for paracorporeal support (71% vs 88%; $P = 0.017$) (Supplementary Material, Fig. S3). If groups with intracorporeal and paracorporeal devices are separated by weight categories, patients >10 kg do not have a significantly different outcome but do differ significantly between weight categories ($P = 0.0022$) (Fig. 8). A comparison of survival rates of patients with or without pre-VAD implant circulatory support (e.g. extracorporeal life support or an intra-aortic balloon pump) reveals that patients with support have a significantly worse outcome ($P = 0.0081$) (Fig. 9). Survival according to the aetiology of

Table 7: Device strategy at the time of first implant, stratified by age categories

Device strategy	<1	1–5	6–10	>10	Total
Bridge to recovery	8	7	2	10	27
Bridge to transplant (patient currently listed for transplant)	28	47	25	90	190
Possible bridge to transplant	16	20	21	47	104
Rescue therapy	2	7	4	15	28
Unknown/other	1	1	1	1	4
Total	55	82	53	163	353

Table 8: Primary causes of death

Primary cause of death	*n* (%)
Neurological dysfunction	26 (38.2)
Multiorgan failure	13 (19.1)
Major bleeding	4 (5.9)
Major infection	4 (5.9)
Cardiopulmonary failure	3 (4.4)
Device malfunction	2 (2.9)
Right heart failure	1 (1.5)
Other	7 (10.3)
Unknown/missing	8 (11.8)
Total	68

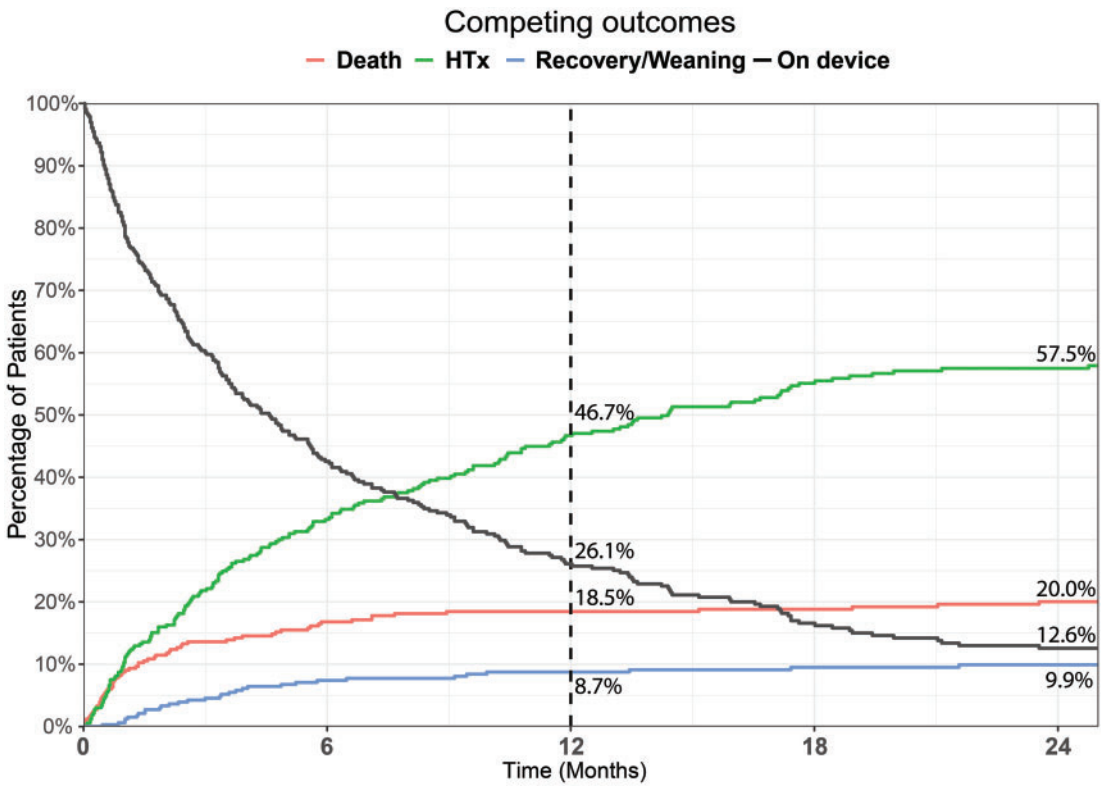

Figure 2: Competing outcomes analysis for death, heart transplant, recovery/weaning or patients on device support. HTx: heart transplant.

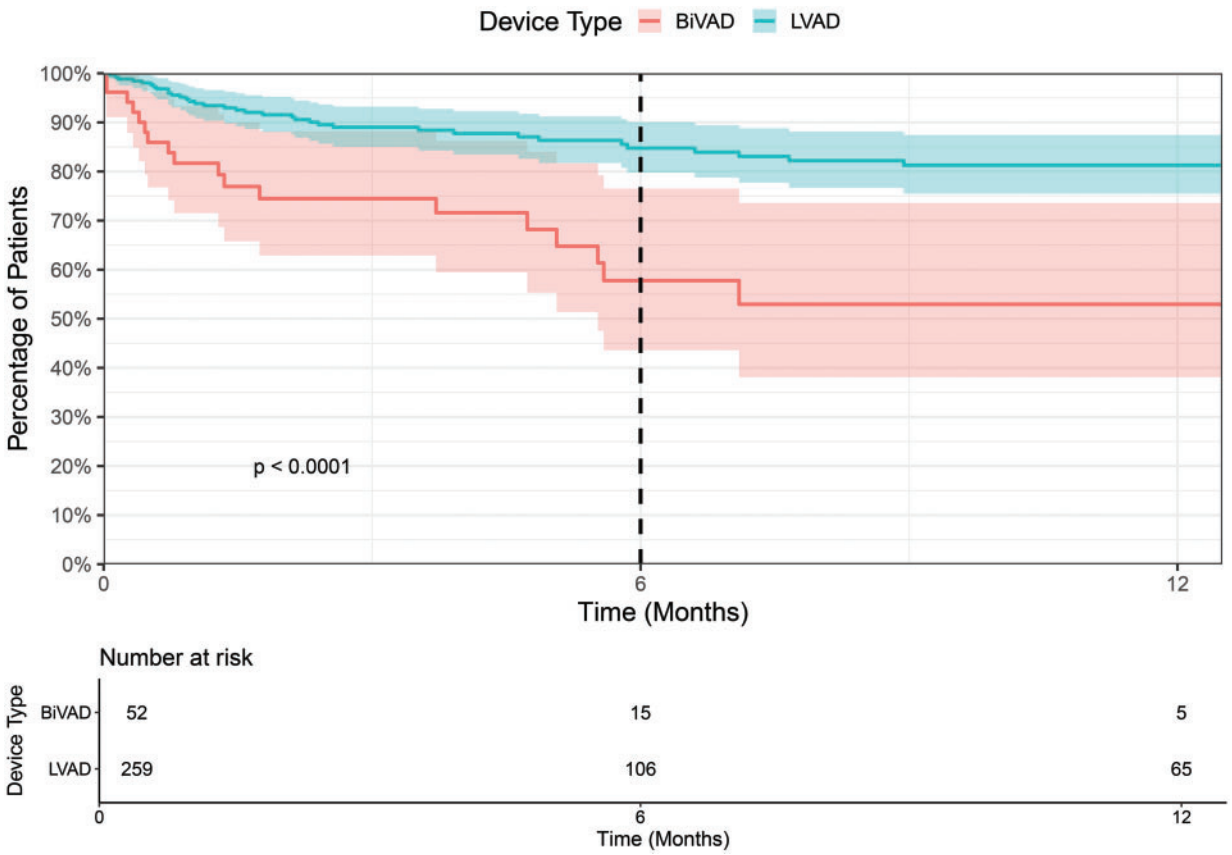

Figure 3: Survival analysis of LVAD versus BiVAD. BiVAD: biventricular assist device; LVAD: left ventricular assist device.

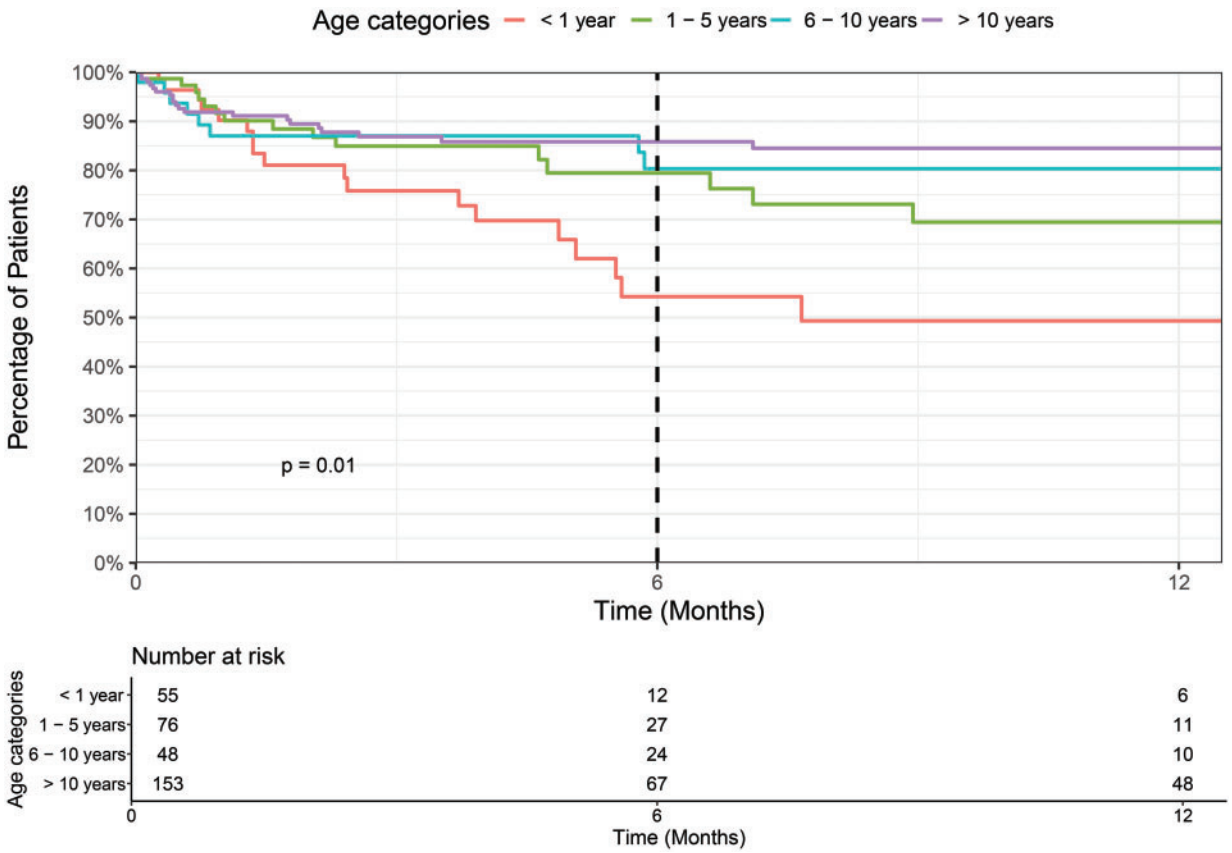

Figure 4: Survival analysis by age category.

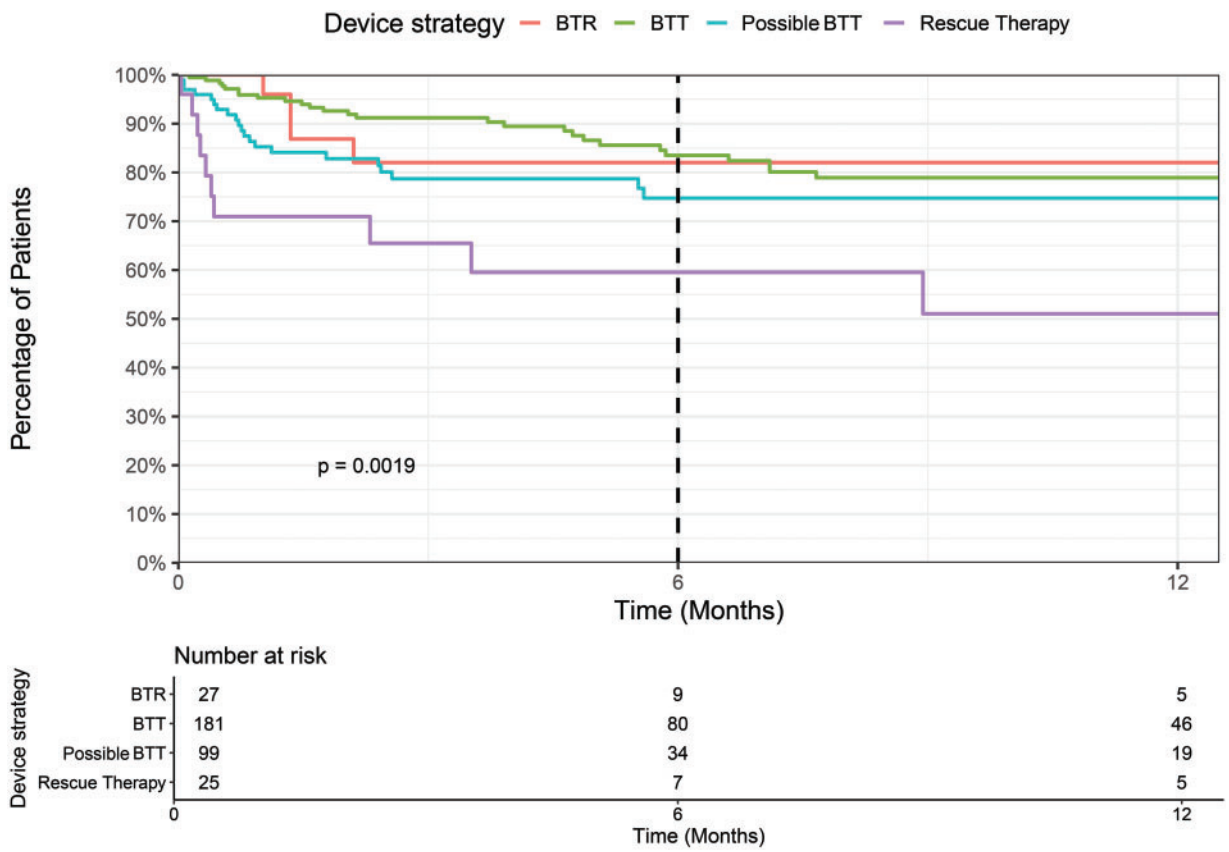

Figure 5: Survival analysis by device strategy. BTR: bridge to recovery; BTT: bridge to transplant.

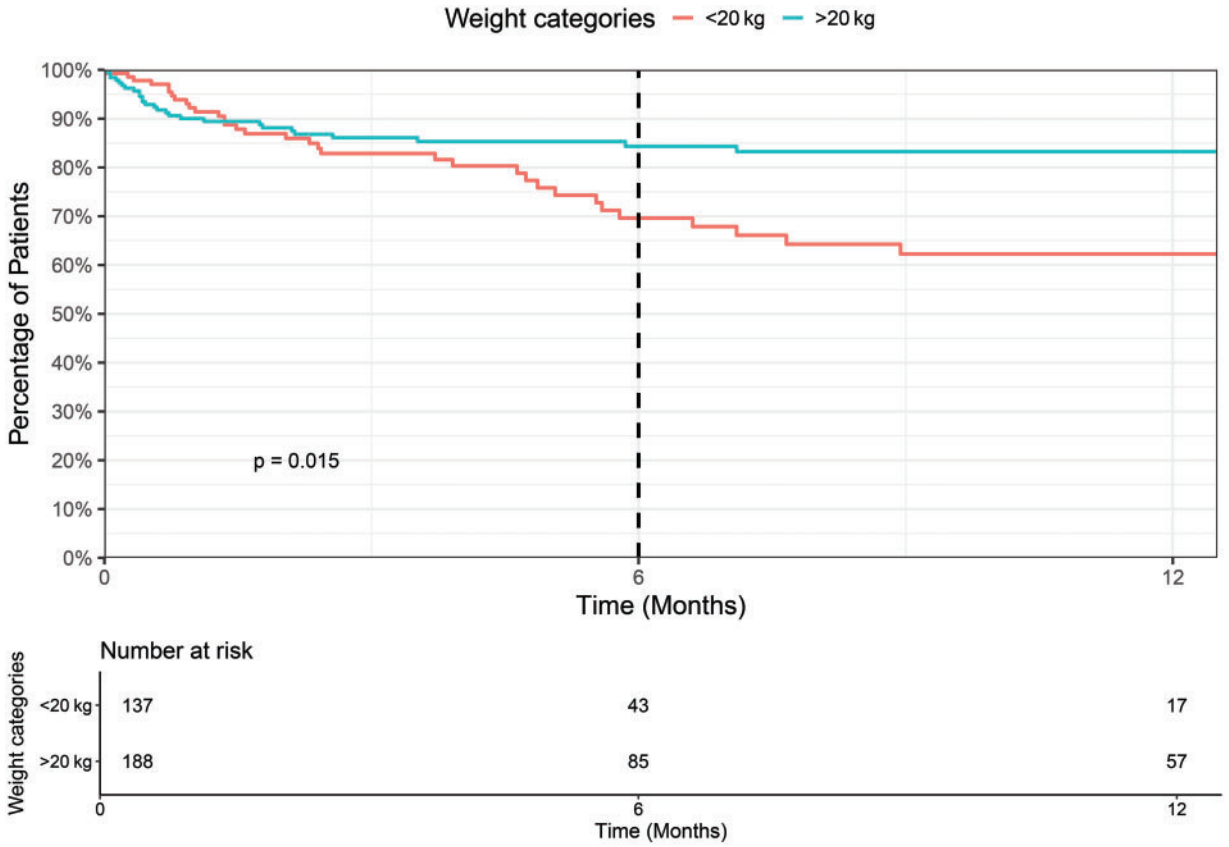

Figure 6: Survival by weight: below 20 kg or 20 kg and above.

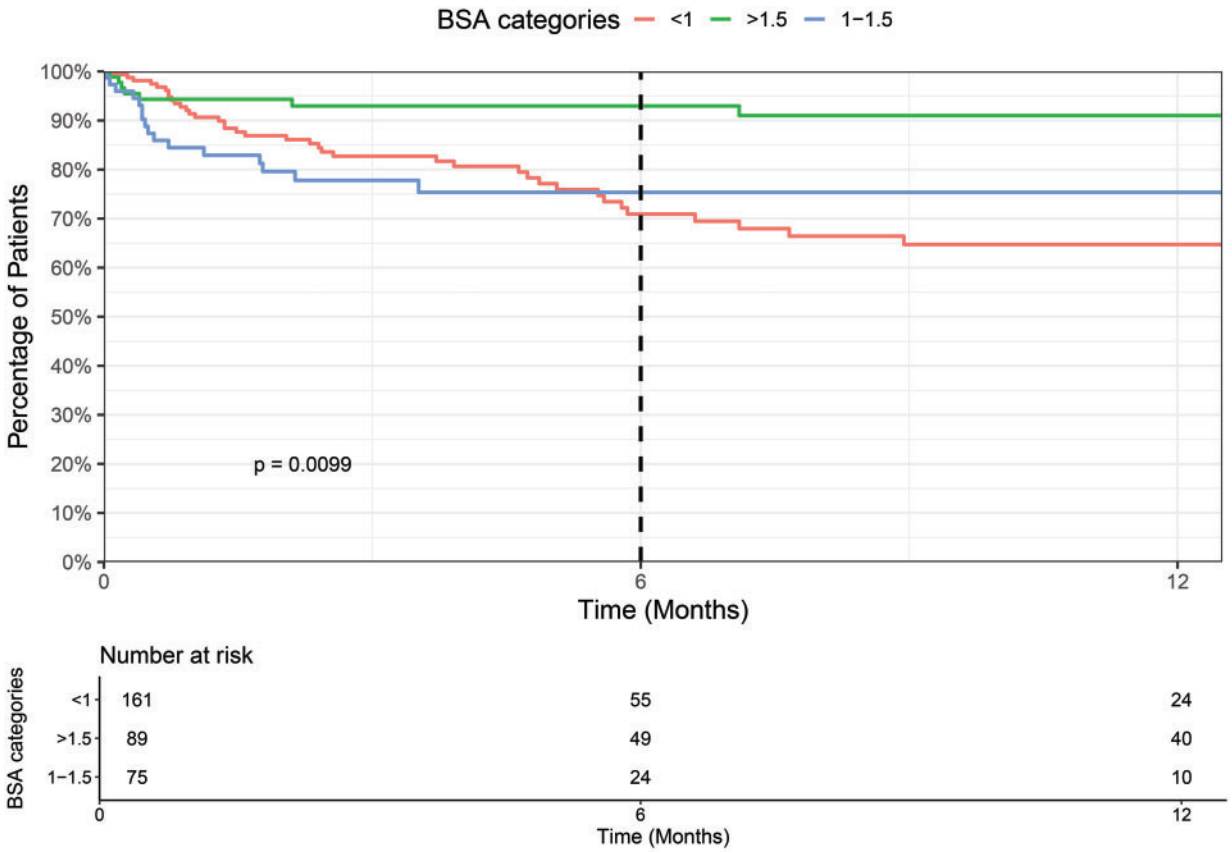

Figure 7: Survival stratified by BSA. BSA: body surface area.

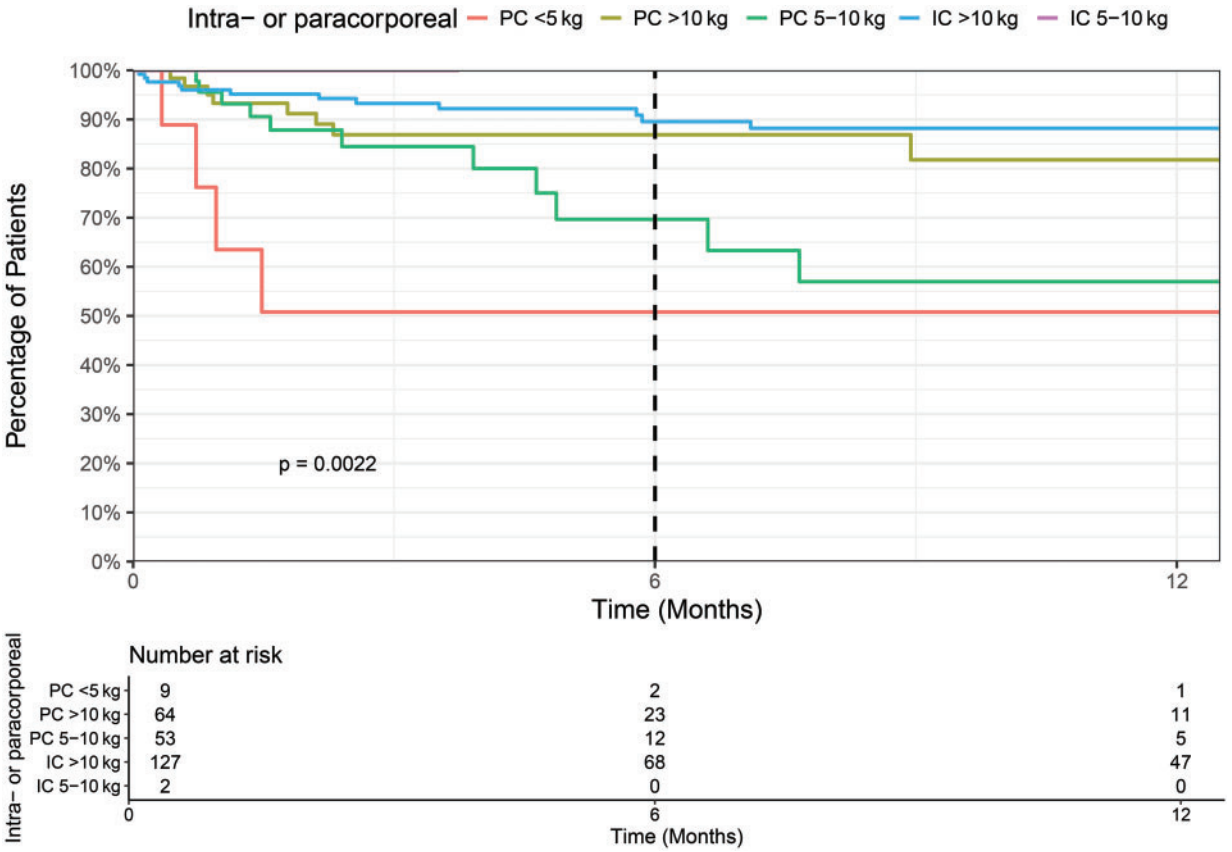

Figure 8: Survival for IC versus PC devices by weight category. IC: intracorporeal; PC: paracorporeal.

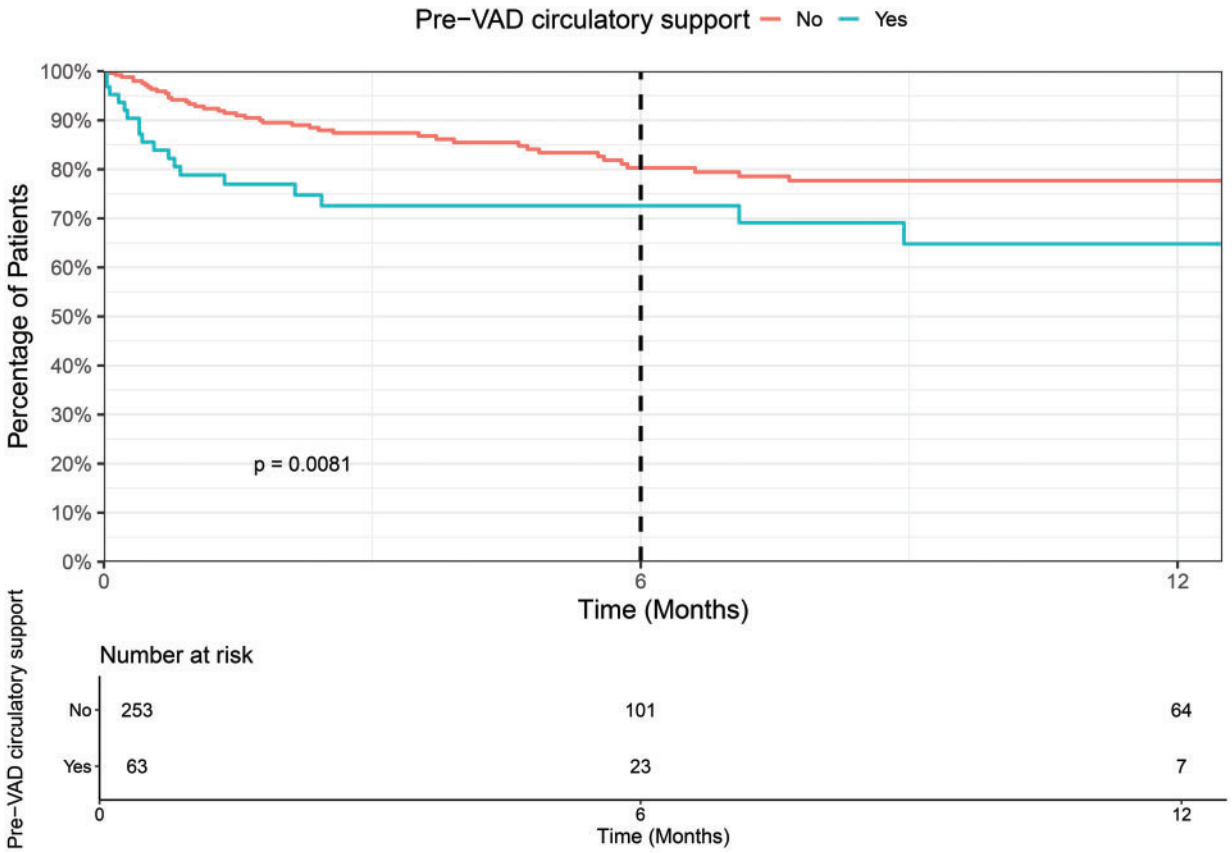

Figure 9: Survival of patients stratified by pre-VAD implant circulatory support. VAD: ventricular assist device.

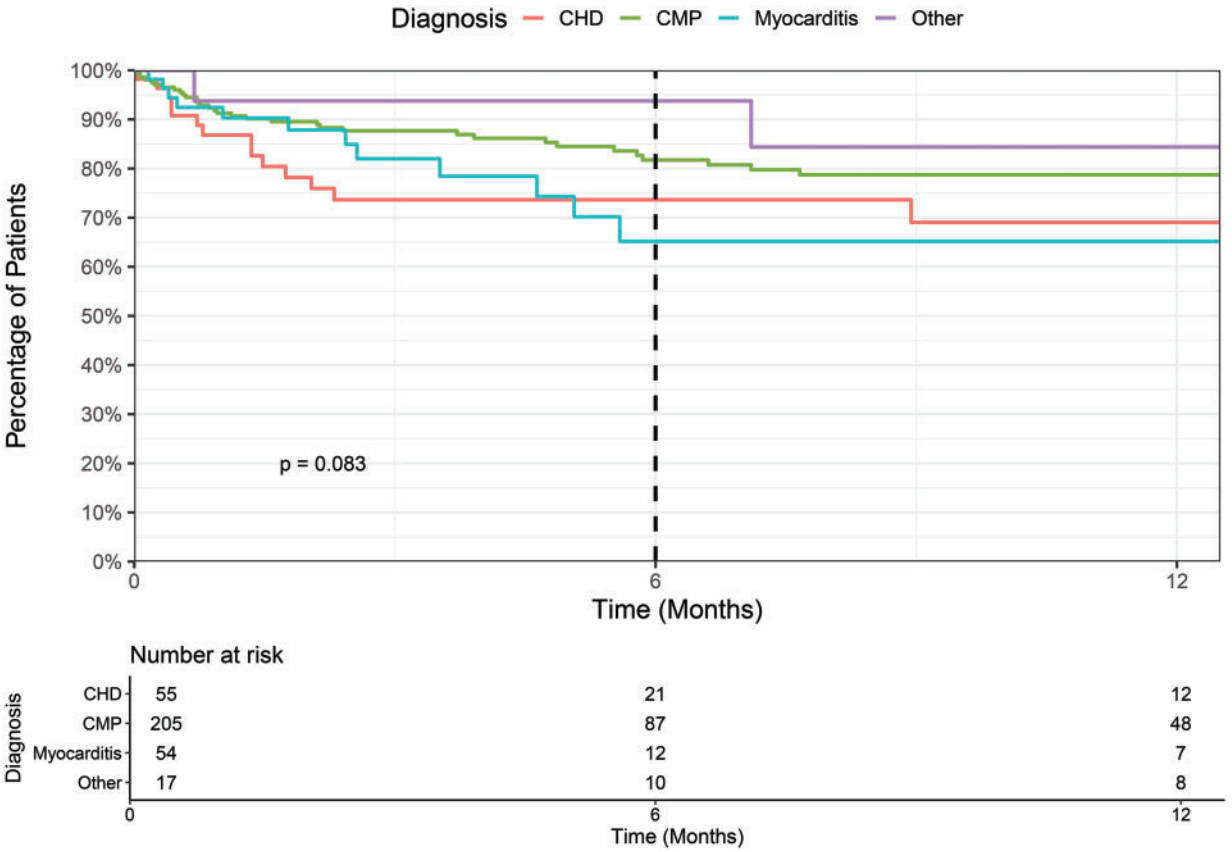

Figure 10: Survival of patients stratified by aetiology of heart failure. CHD: congenital heart disease; CMP: cardiomyopathy.

Table 9: Univariable and multivariable analyses of baseline predictors for death

Characteristics	Univariable		Multivariable	
	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
Age (years)				
<1	Reference		Reference	
1–5	0.51 (0.25–1.06)	0.07	0.40 (0.19–0.84)	0.02
6–10	0.39 (0.17–0.89)	0.03	0.48 (0.21–1.09)	0.08
>10	0.28 (0.14–0.55)	< 0.001	0.32 (0.16–0.64)	0.001
Device strategy				
Bridge to transplant	Reference		Reference	
Bridge to recovery	1.07 (0.38–2.99)	0.89	1.08 (0.38–3.06)	0.88
Rescue therapy	2.82 (1.38–5.77)	0.004	3.24 (1.56–6.74)	0.002
Device type				
BiVAD	Reference		Reference	
LVAD	0.33 (0.19–0.58)	<0.001	0.37 (0.20–0.68)	0.001

BiVAD: biventricular assist device; CI: confidence interval; LVAD: left ventricular assist device.

Table 10: Major adverse events

Major adverse events	Within 3 months		After 3 months		Total
	Event counts	Events per patient-year	Event counts	Events per patient-year	
Device malfunction	106	1.69	107	0.60	213
Major bleeding	30	0.48	7	0.04	37
Major infection	40	0.64	62	0.35	102
Neurological dysfunction	49	0.78	24	0.13	73
Total	225		200		425

heart failure did not reveal a statistically significant difference ($P = 0.083$) (Fig. 10).

An univariable Cox regression model revealed that older patients and patients supported by an LVAD (compared to BiVAD) [hazard ratio (HR) 0.33, 95% confidence interval (CI) 0.19–0.58; $P = 0.001$] had a significantly lower risk of death, whereas patients with device strategy rescue therapy had a significantly higher risk of death (HR 2.82, 95% CI 1.38–5.77; $P = 0.004$) (Table 9). These findings were confirmed in a multivariable model. Compared to patients <1 year old, the HR for death was statistically significant for patients aged 1–5 years: 0.40 (95% CI 0.19–0.84; $P = 0.02$) and for patients >10 years: 0.32 (95% CI 0.16–0.64; $P = 0.001$) and trended towards significance for patients aged 6–10 years (HR 0.48, 95% CI 0.21–1.09; $P = 0.08$) (Table 9). Rescue remained a predictor for a significantly worse survival rate (HR 3.24, 95% CI 1.56–6.74; $P = 0.002$), whereas the use of an LVAD was associated with a lower probability of death (HR 0.37, 95% CI 0.20–0.68; $P = 0.001$).

Adverse events

Overall, 425 adverse events were reported during VAD support. Within the first 3 months after VAD implantation, 225 events occurred whereas 200 occurred after 3 months (Table 10).

The most frequently reported major adverse event was device malfunction, which included, as per definition, pump exchanges from paracorporeal devices due to pump thrombosis. Device malfunction occurred 106 times in the first 3 months, which resulted in 1.69 events per patient-year. After 3 months, 0.60 device malfunctions per patient-year were reported.

The event rates for neurological dysfunction and infection were 0.78 ($n = 49$) and 0.64 ($n = 40$) per patient-year, respectively, for the first 3 months. After 3 months, 0.13 events of neurological dysfunction ($n = 24$) and 0.35 infections per patient-year ($n = 62$) were reported. Finally, 30 events of major bleeding were reported in the first 3 months (0.48 events per patient-year) and 7 events after 3 months (0.04 events per patient-year).

DISCUSSION

This second Paedi-EUROMACS report is an update of the previous report, but it simultaneously explores some outcomes in more detail. In comparison to the first report, the number of registered paediatric implants increased from 210 to 353, whereas the baseline demographic characteristics remained relatively unchanged. This growth is caused by the continuous inclusion of patients in centres that were already participating but is also the result of new centres that started to contribute data to EUROMACS. Twenty-nine centres contributed data to this second paediatric report, an increase of 20%. Device strategies as well as device characteristics have not changed considerably [1].

Comparing the data with those of the North American Pedimacs Registry reveals relatively similar baseline characteristics in respect to age, devices implanted, device strategy and aetiology of heart failure. However, some differences should be noted. First, in Pedimacs, a larger percentage of patients had INTERMACS patient profile 1 (33%) vs 21% in our study [2]. Furthermore, the percentage of patients requiring mechanical ventilation prior to VAD implantation was reported to be almost

twice as high in Pedimacs (45% compared to 25.3% in Paedi-EUROMACS). Extracorporeal life support prior to a VAD implant was 17.2% in this study, whereas it was 12.6% for Pedimacs (but only for those implanted with a continuous flow device) [3].

If we continue comparing outcomes in this report to those in the first report, we see that approximately the same percentage of patients has recovered or had a transplant after 2 years and the same holds true for the percentage of patients who died. In comparison to Pedimacs though, there remains a striking difference in early transplant rates, with ≈50% of the patients having transplants after 6 months in North America, whereas fewer than 35% had transplants in our current study. Of interest, though, is the fact that after 12 months of VAD support, differences in the rates of transplants have become smaller: 51.4% in Pedimacs and 46.7% in Paedi-EUROMACS, an improvement compared to the analysis in the first report (38%) [1].

Adverse events rates in this study are considerably higher than those reported in the first report. One explanation for this increase could be that the additional patients in this second report were sicker and encountered more adverse events. However, as previously mentioned, the baseline characteristics of the patients discussed in this report do not differ considerably from those studied in the previous report, making this an unlikely explanation. Furthermore, the current adverse event rates are in a range comparable to the rates reported in North America. For instance, device malfunction was reported to be 2.4 events per patient year in the first 3 months, whereas this report has a 1.69 event rate per patient-year. The cause of device malfunction is infrequently registered within the EUROMACS follow-up.

In this second paediatric report, some specific subgroups were studied more closely. The analysis of patients in era I compared to that of patients in era II did not reveal any significant differences except for the fact that fewer BiVAD set-ups were implanted in era II than in era I (8.6% vs 23.7%, respectively). Survival rates were similar for era I and era II, which indicates that, although the experience with the devices has increased over the years, outcomes have not. A recent study based on the Berlin Heart EXCOR prospective registry did find a significantly improved survival rate for patients weighing <10 kg implanted from 2013 to 2017 compared to those implanted from 2000 to 2012 [4]. However, that study considered eras different from those compared in our current study. In addition, improvements in the design of the Berlin Heart EXCOR were implemented from 2000 to 2012, including the addition of a 15-ml stroke volume chamber [5, 6].

When considering patients in different age categories, it is apparent that younger patients have worse outcomes than older patients, which was confirmed in the multivariable analysis. This difference is especially striking for patients below the age of 1 year compared to the other groups, with a 6-month survival of 54.3% compared to survival percentages ranging from 79.4% to 85.8% for the age categories >1 year. These results are similar to those of the North American experience (≈50% survival at 6 months <1 year) [2] and highlight that there is still much room for improvement in this select population.

Similarly, patients weighing <20 kg did significantly worse than those weighing>20 kg. These results are in line with those of a previous report that showed that patients weighing <5 or 10 kg had worse survival rates [7, 8]. Furthermore, it is interesting to note that survival for paediatric patients >10 kg did not differ significantly between those with paracorporeal and intracorporeal devices. This result would indicate that the main reason for a worse outcome is not the type of VAD, which is similar to the conclusions of previous reports [9].

Furthermore, patients with a small BSA (<1 m^2) had lower survival rates than patients with a BSA higher than 1 m^2. It was previously reported that a mismatch of the size of the stroke volume chamber of the Berlin Heart EXCOR with BSA is associated with an increase in thromboembolic events but not in the number of deaths [6]. Unfortunately, these data are rarely available in EUROMACS, which makes a granular analysis of such an association not possible.

Finally, outcomes by aetiology showed a trend towards poorer outcomes for patients with myocarditis as the aetiology of heart failure, although patients with congenital heart disease had only a marginally better outcome at 12 months (69% vs 65% survival). This interesting observation is different from previously reported data, where congenital heart disease was associated with the poorest survival rate [3, 8].

Limitations

The registry continues recruiting to increase the numbers of contributing centres, the goal being to include as many European centres as possible. In contrast to the situation in the USA, participation in EUROMACS is not mandatory in Europe. Therefore, surveillance and improvement of data quality are ongoing efforts.

CONCLUSION

The current report shows that there has been an overall improvement of transplant rates at 1 year and that VAD therapy is a viable option for paediatric patients with severe heart failure, with 80% of the patients receiving transplants, weaned or ongoing at 2 years. Furthermore, the European experience is in many ways comparable to the North American experience; however, transplant rates at 6 months remain more advantageous in the Pedimacs cohort. Adverse event rates, however, remain high: Almost 40% of the deceased patients died of neurological adverse events. Moreover, results in young and small children are considerably worse than results in the other groups. Finally, we compared era 1 with era 2 to determine if experience with the devices has resulted in better outcomes. Unfortunately, our analysis does not show an improvement of outcomes over time.

To answer some of the questions as to why some subgroups perform significantly worse than other groups, a paediatric subcommittee of EUROMACS has been set up. Embedded in the European Association for Cardio-Thoracic Surgery Quality Improvement Programme, this committee will identify if and what data fields have to be changed within the registry and will set out study proposals for the contributing hospitals to participate in. This effort will hopefully result in the availability of new data for making clinical decisions for the special population of paediatric patients.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

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