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REPORT

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

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Abstract

OBJECTIVES: EUROMACS is a registry of the *European Association for Cardio-Thoracic Surgery* (EACTS) whose purpose is to gather clinical data related to durable mechanical circulatory support for scientific purposes and to publish annual reports. Because the treatment of children with end-stage heart failure has several significantly different characteristics than the treatment of adults, data and outcomes of interventions are analysed in this dedicated paediatric report.

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 31 December 2017 were analysed. This report includes updates of patient characteristics, implant frequency, outcome (including mortality rates, transplants and recovery rates) as well as adverse events.

RESULTS: Twenty-five hospitals contributed 237 registered implants in 210 patients (81 ♀, 129 ♂) to the registry. The most frequent diagnosis was any form of cardiomyopathy (71.4%) followed by congenital heart disease (18.6%). Overall mean support time on a device was 11.6 months (±16.5 standard deviation). A total of 173 children (82.4%) survived to transplant, recovery or are ongoing; 37 patients (17.6%) died while on support within the observed follow-up time. At 12 months 38% of patients received transplants, 7% were weaned from their device and 15% died. At 24 months, 51% of patients received transplants, 17% died while on support, 22% were on a device and 9% were explanted due to myocardial recovery. The adverse events rate per 100 patient-months was 0.2 for device malfunction, 0.05 for major bleeding, 0.06 for major infection and 0.03 for neurological events within the first 3 months after implantation.

CONCLUSIONS: The first paediatric EUROMACS report reveals a low transplant rate in European countries within the first 2 years of implantation compared to US data. The 1-year survival rate seems to be satisfactory. Device malfunction including pump chamber changes due to thrombosis was the most frequent adverse event.

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

†The first two authors contributed equally to this study.

INTRODUCTION

The use of durable mechanical circulatory support (MCS) in children in the form of a ventricular assist device (VAD) has increased dramatically over the years and has improved survival for paediatric patients on the waiting list for a heart transplant [1]. Paediatric patients receiving MCS is a unique area of study due to the physical size of the recipient, which not only requires careful selection of an appropriately sized device but also different management techniques than those used in adults. Children require specially adapted pharmacological treatment and the prevention of adverse events requires a very different clinical management from that in adults.

The EUROMACS Committee of the *European Association for Cardio-Thoracic Surgery* (EACTS) governs the registry, which was launched in 2009 and became operational in 2012. EUROMACS is the only European-based durable MCS registry for all devices with the CE Marking implanted in children and adults (Table 1). The purpose of the registry is to gather clinical data related to durable MCS for scientific purposes and to publish annual reports. From the outset, all possible options in MCS strategy with respect to devices on the market and to data on patients of every age and geographic area were included [2]. This approach enables the registry not only to select paediatric patients as a distinguished patient cohort for analyses of baseline data but also to follow them up even after they have passed the age of 19 years. EUROMACS collects data continuing through the period of VAD support; there are 3 end points: transplantation, weaning and death. The EUROMACS database has been designed in such a way that the patient and the device outcomes will be comparable with the Pedimacs and Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) databases.

So far, 2 EUROMACS reports have been published [2, 3] analysing the adult population. This EUROMACS report is the first to focus on patients ≤19 years of age. Its goal is to report outcomes of children supported with MCS from a European perspective.

Table 1: Present CE-marked mechanical circulatory support systems registered in the EUROMACS database

MCS type	
Durable devices	
Continuous flow	Berlin Heart INCOR
	CircuLite SYNERGY[a]
	HeartAssist 5
	HeartWare HVAD
	Jarvik 2000
	MicroMed DeBakey
	Thoratec HeartMate II
	Thoratec HeartMate 3
Pulsatile extracorporeal	Berlin Heart EXCOR
	Thoratec PVAD
Total artificial heart	SynCardia Cardiowest
Short-term devices	Abiomed AB5000
	Medos DeltaStream[b]
	Levitronix CentriMag[b]
	Maquet CARDIOHELP[b]

[a]Withdrawn from the market in 2014.

[b]These short-term devices can be used with an oxygenator for extracardiac life support/extracellular membrane oxygenation. A provision has been made for devices that were implanted concomitantly (e.g. a temporary right ventricular assist device) with a durable device.

CE: European conformity; EUROMACS: European Registry for Patients with Mechanical Circulatory Support; MCS: mechanical circulatory support.

METHODS

As per 31 December 2017, 25 centres from 14 different countries (Table 2) submitted to EUROMACS data on patients ≤19 years of age. The participating centres are advised to enter data (of the patients or of the parents who have given consent in writing) of the patients who received an MCS device since 1 January 2011. Thus, newly enrolled centres will retrospectively enter data through that date. Some centres have chosen to submit data from an earlier date, and 35 patients were registered before 1 January 2011.

Data quality checks and audits

To ensure the best quality of data and to exclude the underreporting of suboptimal outcomes, the EUROMACS Registry applies several methods. Incoming data are analysed on a regular basis. Individual hospitals are approached, and guidance is offered to complete or correct their data. Entries are adapted to adhere to the standard. Twice a year, each centre receives a file in which an overview of patients whose statuses need to be updated and whose changes/answers have to be monitored is presented. Statistical consistency and plausibility checks are performed, and the records containing the inconsistent data of the participating centres are identified. Data that are not plausible require checking and confirmation by the participating centres.

Table 2: Participating paediatric units providing data for this report

Country	City, hospital
Austria	Innsbruck, Innsbruck University Clinics
Belarus	Minsk, Republican Scientific and Practical Center Cardiology
Belgium	Gent, Universitair Ziekenhuis Gent
	Leuven, Universitair Ziekenhuis UZ Leuven
Czech Republic	Brno, Center for Cardiovascular and Transplant Surgery
	Prague, Institute for Clinical and Experimental Medicine
France	Le Plessis Robinson, Centre Chirurgical Marie-Lannelongue
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	Rome, Ospedale Pediatrico Bambino Gesù
	Bergamo, Ospedale Papa Giovanni XIII
	Bologna, San Orsola Hospital
	Torino, Regina Margherita Children's Hospital
Kazakhstan	Astana, National Research Cardiac Surgery Center
Netherlands	Rotterdam, Erasmus Medisch Center
	Utrecht, Universitair Medisch Centrum Utrecht
Poland	Warsaw, Childrens Memorial Hospital
Spain	Madrid, Hospital La Paz
Switzerland	Zürich, Kinderspital Zürich
	Bern, University Hospital Bern (Inselspital)
Turkey	Ankara, Baskent University Hospital
	Izmir, Ege University Hospital
	Istanbul, Florence Nightingale University Hospital

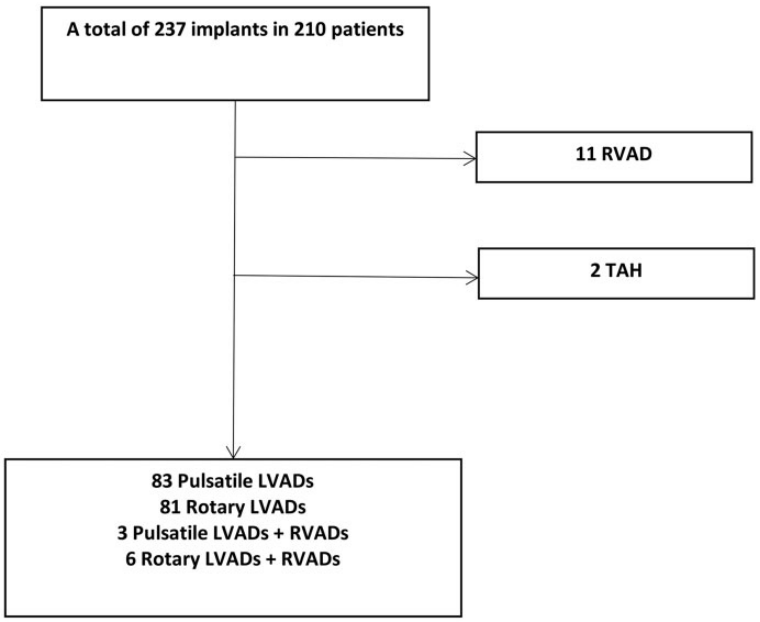

Figure 1: Paediatric patients registered in the EUROMACS Registry. LVAD: left ventricular assist device; RVAD: right ventricular assist device; TAH: total artificial heart.

The average number of follow-up records per patient is calculated on a per centre basis and serves as an indicator for homogeneity and completeness of recording. In addition, random on-site audits of participating centres are carried out.

Statistical analysis

We checked for the chronological plausibility of the records and eliminated or corrected implausible records by queries to on-site data managers. Data are presented as the mean ± the standard deviation (SD) or frequency with percentage. To examine mortality after implant, Kaplan–Meier estimates of cumulative probabilities were calculated, including 95% confidence intervals as a measure of certainty, because we did not truncate the curves. Kaplan–Meier curves were censored at explantation due to transplant or recovery. A patient is considered at risk until explantation because the patient received a transplant, has been weaned from the device, has died or is alive. To determine these values, cumulative incidences were calculated using competing outcomes methods and are presented for the first 2 years after the device is implanted. To avoid any censored individuals, only patients with a follow-up period of 2 years were considered for the competing outcome analysis. The user-written programme 'STCOMPET' in STATA was used to calculate the cumulative incidence [4]. Statistical analyses and figures were constructed using Stata 15.0 (StataCorp, College Station, TX, USA).

RESULTS

Patient population

Between January 2000 and December 2017, 237 implants in 210 patients were registered (Fig. 1), 129 (61.4%) of which were male and 81 (38.6%) of which were female. The mean age was 9.3 years (±7.0 SD), and it ranged from 0 weeks to 19 years. Almost one-fifth of the patients were below 1 year of age, and half of the population was above 10 years of age. Baseline characteristics can be seen in Table 3. Primary diagnoses at admission included cardiomyopathy (including myocarditis) in 150 (71.4%), congenital heart disease in 39 (18.6%) and other in 21 (10%) (Table 4). VAD implantation was performed primarily in patients with INTERMACS levels 1, 2 and 3 with 44 (21.0%) patients at INTERMACS profile 1.

A total of 70.5% of all children were on inotropic support prior to VAD implantation. Extracardiac life support was used in 17.6% of the patients prior to VAD implantation. Twenty-two patients received a 2nd VAD implant after the 1st one, 3 patients a 3rd and 2 patients a 4th implant (Table 5). The majority of the patients (73.8%) were treated with the intention to transplant (i.e. bridge to transplant or possible bridge to transplant), and this was true for all age groups (Table 6).

Table 3: Patient characteristics preimplant

Characteristics	Total (*n* = 210)
Age (years), mean ± SD (median, range)	9.3 ± 7.0 (10.5, 0–19)
Preoperative creatinine level (mg/dl), mean ± SD (median, range)	0.83 ± 0.51 (0.70, 0.19 – 3.74)
Preoperative total bilirubin level (mg/dl), mean ± SD (median, range)	0.1 ± 0.1 (0.06, 0.001–0.9)
Body mass index (kg/m^2), mean ± SD (median, range)	17.87 ± 5.08 (16.4, 9.78–37.65)
Age categories, *n* (%)	
<1 year	38 (18.1)
1–5 years	45 (21.4)
6–10 years	22 (10.5)
>10 years	105 (50.0)
Total	210
Gender, *n* (%)	
Male	129 (61.4)
Female	81 (38.6)

SD: standard deviation.

A total of 46.8% of the patients were supported with the Berlin Heart Excor® (Berlin Heart, Berlin, Germany), 5.9% with the Heart Mate II® (Thoratec Corp., Pleasanton, CA, USA), 0.8% with HeartAssist5® (MicroMed, Houston, TX, USA) and 27.0% with HeartWare HVAD® (HeartWare Ltd., Framingham, MA, USA) (Table 7). In 67 patients, a concomitant cardiac procedure (21 congenital and valve procedures and 46 other procedures) was performed.

Outcomes

The mean support time on a device was 11.6 months (±16.5 SD). The mean stay in the intensive care unit was 37.0 days (±54.5 SD). Ninety-three (44.3%) patients were discharged either to their homes or to a rehabilitation facility. A total of 173 children (82.4%) survived to transplant, recovery, or are on ongoing treatment until the last follow-up. At 6 months, 33% of the patients and at the 1st year 38% of the children received a transplant. This percentage climbed to 51% at 2 years post VAD implantation. Thirty-seven patients (17.6%) died while on support within the observed follow-up time (Table 8).

A total of 37 patients (17.6%) died, of which 24.3% died of cerebrovascular accidents. Five patients (13.5%) died of multiorgan failure. The primary cause of death was not specified for 14 patients (Table 9).

Survival

Event-free survival of all paediatric patients on MCS was 81% at 6 months, 78% at 12 months and 66% at 2 years with censoring at time of explantation for transplant or recovery (Fig. 2). When stratified by device type, i.e. left ventricular assist device (LVAD) or a biventricular assist device, 81% survival was observed in the 1st year for LVADs and 63% for biventricular assist devices ($P = 0.06$) (Fig. 3).

When stratified by age, the oldest age group (11–19 years) had an 86% survival rate at the end of the 1st year and 76% at the end of the 2nd year; the age group 6–10 years had an 86% 1-year and 72% 2-year survival rate and the age group 1–5 years had a 69% survival rate at the end of the 1st year and 55% at the end of the 2nd year. Patients ≤1 year old showed the poorest outcome: 54% had a 1-year and 43%, a 2-year survival rate (Fig. 4). However, the latter survival rates showed poor statistical significance ($P = 0.22$). Figure 5 shows the survival rate stratified by device strategy.

Table 4: Primary diagnosis

Diagnosis	*n*	%
Cardiomyopathy	117	55.7
Myocarditis	33	15.7
Congenital heart disease	39	18.6
Coronary artery disease	1	0.5
Valvular heart disease	3	1.4
Cancer	1	0.5
Unknown/missing	16	7.6
	210	

Table 5: Primary and subsequently implanted devices

Devices	1st	2nd	3rd	4th	Total
BiVAD	36	2			38
LVAD	163	12	1		176
LVAD and RVAD	8	1			9
RVAD	1	6	2	2	11
Total artificial heart	1	1			2
Unknown	1				1
Total	210	22	3	2	237

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

Table 7: Type of ventricular assist devices per age group

	<1	1–5	6–10	>10	Total
LVAD alone					
Pulsatile	32	30	7	14	83
Continuous	2	2	9	68	81
Unspecified		1	1	10	12
LVAD, temporary RVAD					
Continuous LVAD, continuous RVAD				6	6
Pulsatile LVAD, continuous RVAD	2	1			3
BiVAD					
Pulsatile	6	11	5	13	35
Continuous			3		3
RVAD	3	3	3	2	11
Total artificial heart					
Pulsatile		2			2
Unknown				1	1
					237

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

Table 6: Device strategy at time of implantation, stratified by age categories

	<1 *n* (%)	1–5 *n* (%)	6–10 *n* (%)	>10 *n* (%)	Total *n* (%)
Bridge to recovery	4 (8.9)	4 (8.0)	2 (7.1)	7 (6.1)	17 (7.2)
Bridge to transplant	18 (40.0)	23 (46.0)	9 (32.1)	51 (44.7)	101 (42.6)
Destination therapy	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.4)
Possible bridge to transplant	14 (31.1)	13 (26.0)	11 (39.3)	36 (31.6)	74 (31.2)
Rescue therapy	3 (6.7)	7 (14.0)	2 (7.1)	7 (6.1)	19 (8.0)
Unknown	6 (13.3)	3 (6.0)	4 (14.3)	12 (10.5)	25 (10.5)
Total	45 (100)	50 (100)	28 (100)	114 (100.0)	237 (100)

Competing outcomes

Within 2 years after an implant, 51% of the patients received a heart transplant and 17% died. Only 9% could be weaned from the device and 22% had ongoing device support (Fig. 6).

Table 8: Current device strategy stratified by the end point

	End point				
	On device	Dead	Received transplant	Weaned	Total
Missing		1	3	1	11
Bridge to recovery	2	2	1	11	16
Bridge to transplant	22	12	60	2	96
Possible bridge to transplant	10	16	38	6	70
Rescue therapy	2	6	5	4	17
Total	42	37	107	24	210

Table 9: Primary cause of death

Primary cause of death	*n*	%
Bleeding	2	5.4
Cardiopulmonary failure	2	5.4
Cerebrovascular accident	9	24.3
Device failure	1	2.7
Multiorgan failure	5	13.5
Other cause of death	1	2.7
Right heart failure	1	2.7
Sepsis	2	5.4
Unknown/missing	14	37.8
	37	

Adverse events

Overall, 151 major adverse events were reported during VAD support. Major adverse events are defined using the INTERMACS definitions [5]. These included infection, device malfunction, bleeding and neurological events (Table 10). Within the first 3 months after VAD implantation, 38 events occurred whereas 113 occurred after 3 months.

The most frequent major adverse event was device malfunction, which included as per definition pump exchanges from extracorporeal devices due to pump thrombosis. Device malfunction occurred 20 times in the first 3 months. In the same period, the device malfunction rate was 0.2 per 100 person-months and 4.2 per 100 person-months after 3 months.

Infections were the 2nd most frequent adverse event ($n = 31$; event rate: 20.5%). Infections were divided into VAD-specific, VAD-related and non-VAD-related.

Major infection in paediatric patients occurred more frequently after the first 3 months post implantation ($n = 23$), i.e. 1.3 events per 100 patients. During the first 3 months, 8 cases, or 0.06 per 100 patients, were reported.

Major bleeding, defined as an episode of suspected internal or external bleeding that resulted in death, reoperation, hospitalization or major transfusion, but not including cerebral haemorrhage, occurred in 15 patients (event rate, 9.9%) with 0.05 events per 100 patients in the first 3 months and 0.5 events per 100 patients after 3 months. Two patients died (0.95%) of a bleeding event.

Neurological events were defined by the occurrence of an ischaemic or a haemorrhagic stroke. Eleven patients had a neurological event (event rate: 7.3%). Whereas only 0.03 events per 100 patients occurred within the first 3 months after implantation, the majority occurred later (0.8 events per 100 patients after 3 months). Nine patients (24.3%) died of neurological events, making this the primary cause of death within the whole cohort (see also Table 9). Six patients had heart transplants or were successfully weaned from the device after a neurological event.

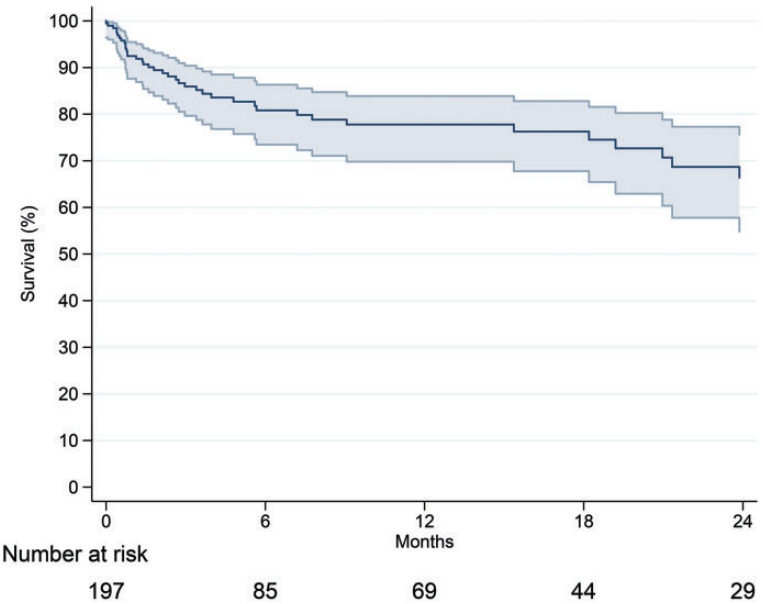

Figure 2: Survival of paediatric patients after primary left or biventricular assist device implantation.

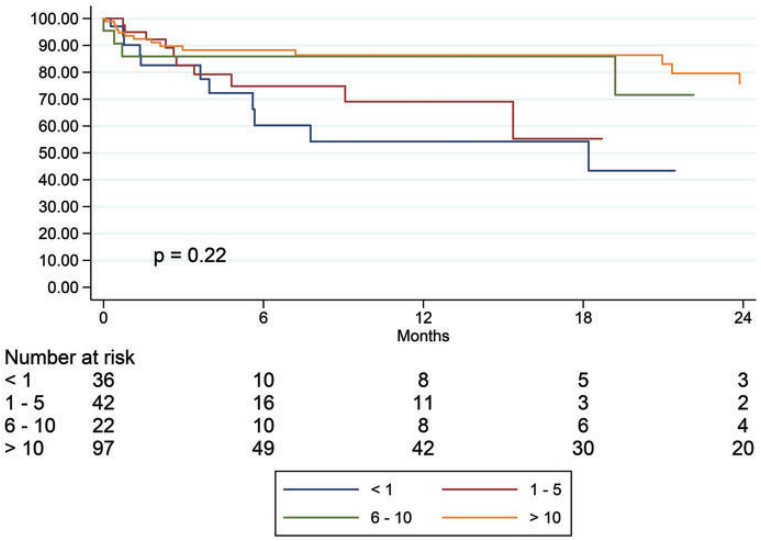

Figure 3: Survival of paediatric patients after primary implantation of a left ventricular assist device or a biventricular assist device, stratified by age.

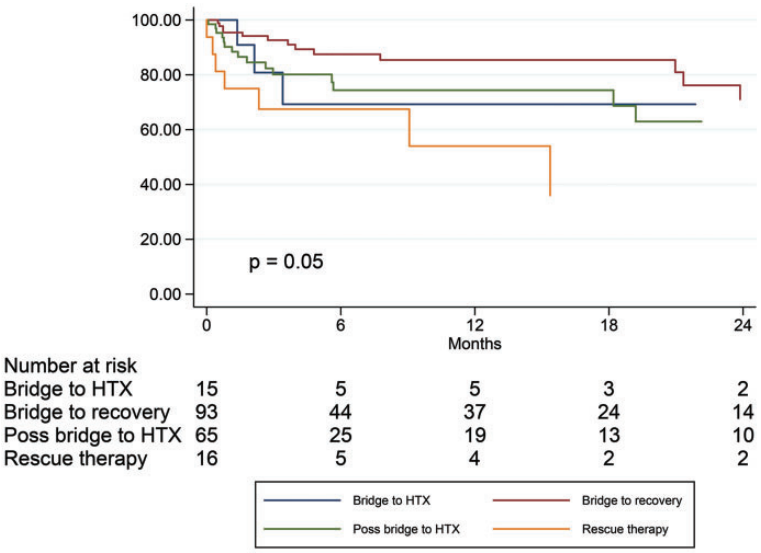

Figure 4: Survival of paediatric patients after primary implantation of a left ventricular assist device or a biventricular assist device, stratified by the device implant strategy used. HTX: heart transplant.

DISCUSSION

This report is the first of children supported with durable MCS that has emerged from the EUROMACS database. The EUROMACS registry is the largest database monitoring children supported with VADs in Europe, and enrolment of centres and patients continues. The authors believe it is crucial to add information about the European cohort to the other paediatric MCS database of similar size, Pedimacs, which is restricted to North American data.

One of the most striking differences between the EUROMACS and the Pedimacs cohorts is the waiting time for a heart transplant. Whereas permanent support has long become a reality for adults, bridge to transplantation or transplantability still remains the highest percentage in intention to treat within the paediatric population. Whereas almost 50% [6] of the paediatric patients in North America had a transplant within the first 6 months after a VAD implant, in Europe, only 33% at 6 months had a transplant and 38% patients at 12 months. These numbers reflect the lack of suitable donor organs in Europe, which leads to significantly longer support times. Especially in small countries or in patients under 5 years of age [7, 8], times on the heart transplant waiting list have increased. In the registry of the Eurotransplant International Foundation, the percentage of paediatric patients who receive transplants is 48% at 6 months and 57% at 12 months (personal communication, J. Smits, Eurotransplant). In Switzerland, the number of paediatric heart transplant candidates between 2009 and 2013 increased by a factor of 4 compared to the previous period [9]. In Italy, the mean time on the waiting list is more than 11 months, and in Poland (all patients), the mean waiting time is 12 months. Especially for small countries, international organ exchange among organ procurement organizations is essential. It has a direct positive impact on the possibility of patients receiving a timely, often life-saving, transplant [8]. The

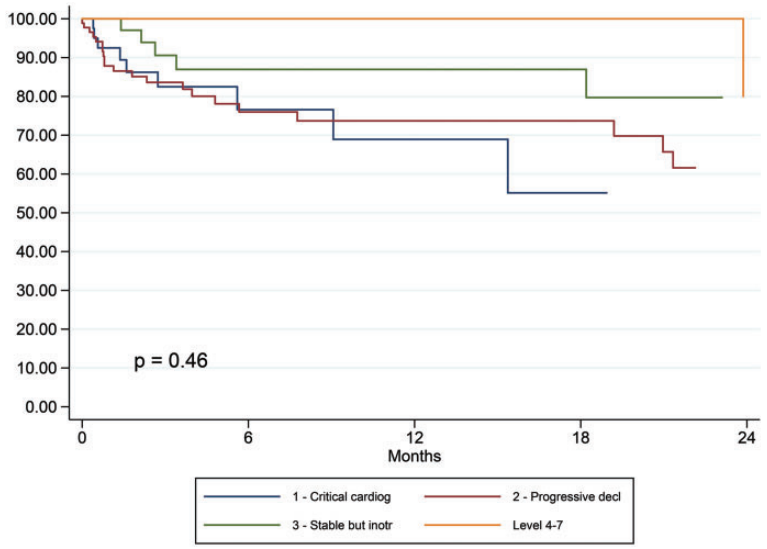

Figure 5: Survival of paediatric patients after primary implantation of a left ventricular assist device or a biventricular assist device, stratified by Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) level.

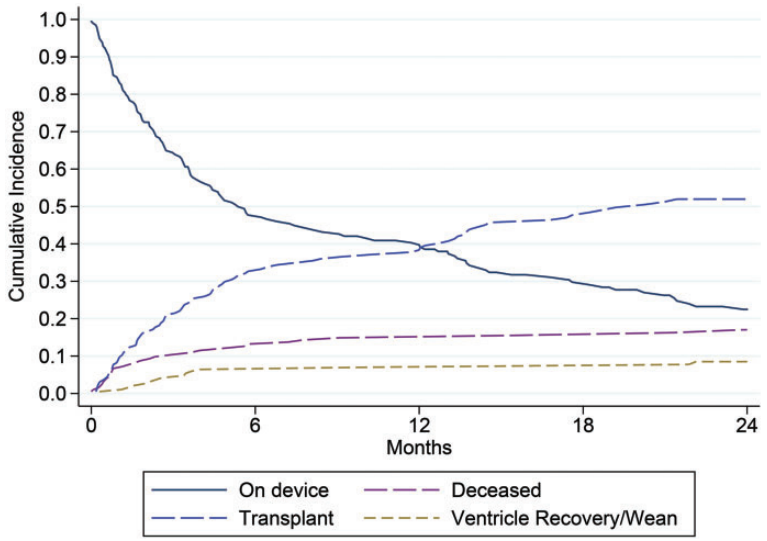

Figure 6: Competing outcomes.

longer support times in Europe enable us to provide outcome data beyond 12 months of support.

One important finding of this report is that the cumulative competing incidence of death is 15% by the end of year 1 and 17% by the end of year 2. This result indicates a low mortality rate in the 2nd year of support and makes permanent support in children more feasible.

A total of 44.3% of the patients were discharged on the device. The methods used for quality checks do not indicate that serious infections are under-reported; in fact, the opposite is true. The percentage is high (20.5%), though the specificity with respect to the severity and location is low, which leads to the suspicion that different definitions may have been used.

The implantation strategy of bridge to recovery is low at 7.3%, which is relatively similar to the percentage published in the Pedimacs report (6.3%). In the group categorized as bridge to recovery ($n = 16$), 11 patients underwent successful explantation (69%). The others are either still on support ($n = 2$), have died ($n = 2$) or received a transplant ($n = 1$). For the whole cohort, 24 patients out of 210 had the device explanted due to weaning (see Table 8). The percentage of devices implanted with the intention to treat for bridge to recovery almost equals the number of devices explanted due to recovery. One reason why this number is so low might be the current lack of standardized guidelines for echocardiographic and haemodynamic criteria for LVAD removal in children [10], although children may have a greater potential for recovery [11] compared to adults.

Adverse events

Neurological events were the leading cause of death in our cohort as well in the North American cohort (24% vs 30%). Blume *et al.* [6] reported a higher stroke rate of 13 early events per 100 patient months and 2 late events per 100 patient months with paracorporeal devices compared to continuous flow devices (3 and 1 events per 100 patient months, respectively). Almond *et al.* [12]

Table 10: Major adverse event rates

	Within 3 months after implant		More than 3 months after implant	
	Event counts	Events per 100 patient months (CI)	Event counts	Events per 100 patient months (CI)
Device malfunction	20	0.2 (0.1–0.3)	74	4.2 (3.4–5.3)
Major bleeding	6	0.05 (0.02–0.1)	9	0.5 (0.3–1.0)
Major infection	8	0.06 (0.03–0.1)	23	1.3 (0.9–2.0)
Neurological event	4	0.03 (0.01–0.09)	7	0.4 (0.2–0.8)
Total events	38		113	

CI: confidence interval.

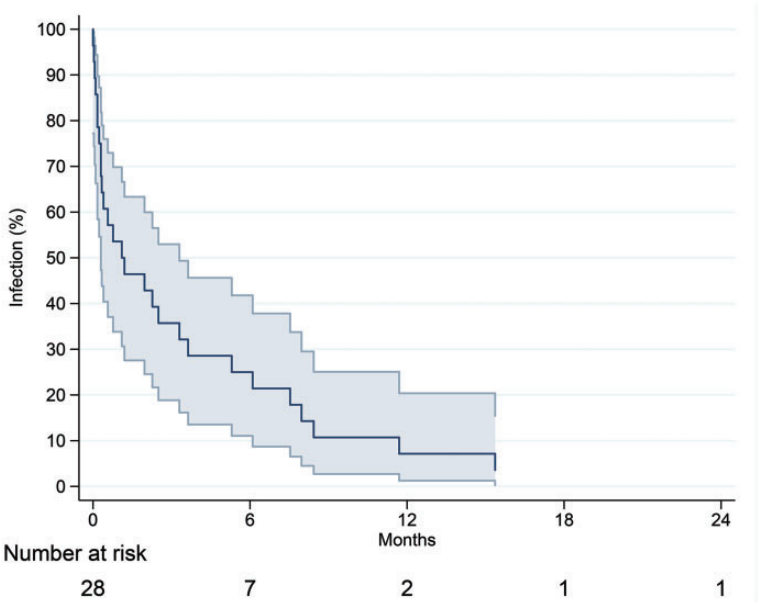

Figure 7: Freedom from infection.

showed comparably high stroke rates for children on EXCOR VADs during the investigational device exemption trial of 15 events per 100 patient years with 29% of children affected. Although the stroke rate was not investigated within this 1st EUROMACS Paediatric Report, a recent study from the paediatric EUROMACS cohort reported low early and late stroke rates with intracorporeal continuous flow devices (0.03 and 0.4 events per 100 patient months, respectively), independent of body surface area [13]. The stroke rates in children on EXCOR and on continuous flow VADs reported in the EUROMACS registry are remarkably low. However, a recent survey addressing the antithrombotic protocols for children on EXCOR VADs in European centres revealed many modifications of the recommended Edmonton protocol with a trend towards more aggressive antithrombotic therapy [14]. Whether these modifications have contributed to lower stroke rates compared to the investigational device exemption trial is under investigation.

Another frequent adverse event was infection in 20.5%, which is clearly high (Fig. 7). One explanation could be that the definition of infection in the EUROMACS registry includes VAD-specific, VAD-related and non-VAD-related infections. The authors found that the major infection rate 3 months post implant was 1.3 per 100 person-months compared to 0.06 per 100 person-months within the first 3 months of implant. This result suggests that many of these infections are less likely to be related to implant surgery and occur while patients remain for prolonged stays in the intensive care unit or during hospitalization post implant. This result could be another effect of the lower transplantation rate and the longer support times in Europe.

Limitations

The present study does not include all European centres that are implanting MCS devices. Besides the contributing centres, 14 additional hospitals were invited to join EUROMACS and submit data. Considering their positive feedback, it is expected that, in a 2nd EUROMACS Paediatric report, the data from most of these 'additional' hospitals will be in the registry. Data collection by means of a registry has per se an important limitation: as in every database, despite all efforts to guarantee data quality and the implementation of audits, under-reporting of adverse events cannot be ruled out.

CONCLUSION

Because EUROMACS is supported by the EACTS, the registry can reach out to an increasing number of participating hospitals to collect baseline and follow-up data on MCS from both adults and children, thus representing European data at the best

achievable level. The ability to specify the different factors contributing to the outcomes of MCS in patients enables paediatric medical professionals to benchmark their data against the results of this study. Many questions remain to be addressed, i.e. discharge, additional specifics in anticoagulation management, focus on congenital heart disease and much more, which were beyond the scope of this 1st paediatric EUROMACS report. Further, a comparison with the 2nd Pedimacs report shows that outcome data differ between the registries. Investigating the reasons for these differences may contribute to insights with respect to treatment modalities and thus provide leads to possible improvements both in Europe and elsewhere.

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