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Cerebral strokes in children on intracorporeal ventricular assist devices: analysis of the EUROMACS Registry

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Abstract

OBJECTIVES: Little is known about cerebral strokes in paediatric patients supported by intracorporeal continuous-flow ventricular assist devices.

METHODS: We retrospectively investigated patients younger than 19 years of age who were treated with an intracorporeal continuous-flow ventricular assist device in the European Registry for Patients with Mechanical Circulatory Support (EUROMACS) database. The patients were stratified by body surface area in Group 1 [<1.2 m^2 (n = 13)] and Group 2 [≥1.2 m^2 (n = 38)]. Cerebral strokes, both ischaemic and haemorrhagic, were studied.

RESULTS: Of the 2941 patients with ventricular assist device (VAD) implants listed in the database, 124 (4%) patients were less than 19 years of age. Fifty-one of them (2%) were supported with a continuous-flow ventricular assist device. Group 1 (6 female and 7 male) had a mean age (±SD) of 9 ± 2.3 years compared with 15.6 ± 1.8 years in Group 2 (21 female and 17 male). Three (23%) patients died in Group 1 on VAD support, whereas 5 (13%) patients died in Group 2 (P = 0.21; log-rank test). Seven (54%) patients with a VAD in Group 1 and 17 (45%) patients in Group 2 underwent transplantation (P = 0.29); of these, 1 (8%) patient recovered (Group 1) with subsequent device explantation. The other patients, 2 in Group 1 and 16 in Group 2, were still on device support at the time of the analysis. There were no cerebral strokes in Group 1, but 4 cerebral strokes (11% of Group 2, 8% of a total of 51 patients in Groups 1 and 2 combined) occurred in Group 2 (3 patients died; P = 0.26; log-rank test). Taken together, the incidence of cerebral strokes in this paediatric cohort of patients with an intracorporeal VAD was 0.1 per patient-year.

CONCLUSIONS: The incidence of cerebral strokes in children with intracorporeal VADs (0.1 per patient-year) seems to be low irrespective of the body surface area.

Keywords: Children • Intracorporeal VAD • Stroke • Neurologic complications

INTRODUCTION

The use of 'durable' long-term mechanical circulatory support in children in the form of a ventricular assist device (VAD) improved survival among those on the heart transplant waiting list [1]. The Berlin Heart EXCOR® has been the mainstay of long-term VAD support for children [2, 3]. One of the major limitations of this device is the high risk of thromboembolic events and the remarkable difficulties in adjusting anticoagulation treatment in infants. Due to the paracorporeal design, patients have been discharged from the hospital only in exceptional cases. One of the devastating complications includes cerebrovascular accidents, such as stroke or haemorrhage, which are reported in 6–62% of patients [4–7]. In recent years, a reasonable number of reports of adults supported with continuous-flow (CF) left ventricular assist devices (LVADs), designed for patients with a body surface area (BSA) >1.2 m^2, have been published [8, 9]. This step has led to improved survival and freedom from stroke and from device malfunction [10]. Data from the Interagency Registry for

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Mechanically Assisted Circulatory Support (INTERMACS) have shown a significant decrease in neurological dysfunction with continuous-flow ventricular assist devices (CFVADs) compared with pulsatile VADs in adults [11]. Because of the obvious advantage of discharging patients on VAD support to home and the observed tendency of patients to resume regular daily activities, these devices have been adopted for paediatric use [12–20]. In the search for anatomical boundaries, the recommended cut-off value of 1.2 m^2 was exceeded. Although implantation in smaller children is feasible from a technical standpoint, few data exist on the outcome, especially on the incidence of cerebral strokes in young patients. One may speculate that in children, where flow rates in the VAD might be lower than in adults, pump thrombosis and thromboembolic events might occur more often. The largest global registry for mechanical circulatory support in children is the Paediatric Interagency Registry for Mechanical Circulatory Support (PediMACS) database, which includes only US patients. Their 2015 report, which focused on children with CFVADs, included 109 patients from 35 hospitals, stated that cerebrovascular stroke or haemorrhage occurred in 26% of patients but without stratification to the body weight or the BSA [21].

Our goal was to investigate ischaemic and haemorrhagic strokes in children supported with intracorporeal CFLVADs based on BSA, using the largest European VAD database [European Registry for Patients with Mechanical Circulatory Support (EUROMACS)]. The aim of this study was to determine the outcome of CFLVADs in children and report the adverse events by focusing on cerebral strokes. This information seems critical for counselling families prior to implantation and managing patients while they are on the device.

METHODS

EUROMACS is an official committee of the European Association for Cardiothoracic Surgery (EACTS). It was created to evaluate the characteristics of implantation and long-term survival and the complications faced by recipients of VADs. EUROMACS contains the data entries of patients of all ages. Data collection continues through the period of implantation of a VAD and concludes with the explantation of the VAD. The EUROMACS database has been designed so that the patient and the device outcomes are comparable with the INTERMACS database. In the meantime, EUROMACS also contributes data to the International Society for Heart and Lung Transplantation Registry for Mechanically Assisted Circulatory Support (IMACS).

This study is a retrospective analysis of the EUROMACS database of patients under 19 years of age who have been provided with an intracorporeal CFVAD. A study proposal was reviewed and granted by the Executive and Extended Board of Directors of EUROMACS (1 April 2015). Data were analyzed for the patients enrolled between 1 January 2009 to 30 June 2016. The patients were stratified by BSA into Group 1 (<1.2 m^2) and Group 2 (≥1.2 m^2). This threshold was chosen because most intracorporeal VADs are approved for patients with BSA ≥ 1.2 m^2.

Study variables

The primary variable was survival until either transplant or recovery. The secondary variables included cerebral strokes and pump thrombosis requiring either pump exchange or conservative treatment. Cerebral stroke was defined by the occurrence of an ischaemic or a haemorrhagic stroke, which was confirmed by neuroimaging.

Statistical analysis

The data are presented as mean ± standard deviation or as a frequency in percentage form. Comparisons were performed using the Student's *t*-test, the Mann–Whitney *U*-test and the Fisher's exact test. Overall, survival and freedom from cerebrovascular events were presented as the Kaplan–Meier curves and compared between the groups using the log-rank test. In addition, the cumulative incidence functions of these competing risks were presented. Statistical analysis was performed using the IBM SPSS Statistics software, version 23.0 (IBM Corp., Armonk, NY, USA) and R (R Development Core Team). A 2-sided *P*-value of 0.05 or lower was considered to indicate statistical significance. The figures were constructed using R, Stata 13.1 (StataCorp, College Station, TX, USA) and Microsoft Excel.

Data quality checks and audits

The EUROMACS Registry applies several methods to ensure the best quality data and to exclude the under-reporting of poor outcomes. Analyses of incoming data are conducted on a regular basis. In addition, 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. A couple of consistency and plausibility checks are performed, and the rendered files containing the inconsistent data of the participating centres are recorded. The data that are not plausible require checking and confirmation by the participating centres. 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. The participating centres undergo random audits.

RESULTS

Patient population

Of the 2941 patients listed in the database as of 30 June 2016, 124 patients at 25 centres (Table 1) were under 19 years of age at the time of implant. Patients on a pulsatile device, biventricular support, extracorporeal centrifugal devices or unspecified implanted devices or those who had missed follow-up visits were excluded. The study group comprised 51 patients (27 boys and 24 girls) from 10 centres. The ethnicity of the patients included 40 Whites, 6 Asians, 2 African Americans and 3 non-defined ethnicities. Dilated cardiomyopathy was the leading underlying disease (Table 2). Six children were on extracorporeal membrane oxygenation, and 88% of all patients were supported on inotropes prior to placement of the VAD. The patients were supported with HeartMate II (Thoratec Corp., Pleasanton, CA, USA; *n* = 6), HeartAssist 5 (MicroMed, Houston, TX, USA; *n* = 2) and HeartWare hVAD (HeartWare Ltd, Framingham, MA, USA; *n* = 42) (see Supplementary Material, File S1). A concomitant cardiac

Table 1: Participating centres that submitted data for children on ventricular assist devices to EUROMACS

Bad Oeynhausen Hospital
Baskent University Hospital
Centre for Cardiovascular and Transplant Surgery Brno
Children's Hospital Zurich
Ege University Hospital Izmir
ESPAMACS, Spain (7 centres)
Freiburg University Heart Clinic
German Heart Institute Berlin
Gottsegen Hungarian Institute of Cardiology
Innsbruck University Clinic
National Research Cardiac Surgery Center—Kazakhstan
Ospedale Papa Giovanni XIII—Bergamo
Republican Scientific and Practical Center Cardiology Minsk
San Orsola Hospital—Bologna
Torino Regina Margherita Children's Hospital
University Heart Center Freiburg, Bad Krozingen
University Hospital Berne
University Medical Center Utrecht
Universitair Ziekenhuis Gent

Table 2: Cardiac diagnosis

		Entire study cohort	Group 1 <1.2 m^2	Group 2 ≥1.2 m^2
Dilated cardiomyopathy		40	9	31
Congenital heart disease	Total	4	3	1
	HLHS[a]	1	1	0
	TGA	1	0	1
	Other	2	2	0
Cardiomyopathy, other		7	1	6

HLHS: hypoplastic left heart syndrome; TGA: transposition of the great arteries.
[a]After Fontan completion; failing Fontan.

procedure (tricuspid valve repair and aortic valve replacement) was performed in only 1 patient. The groups did not show any differences in demographic variables (disregarding age, height and weight per the definition), except for the INTERMACS profile (Table 3 and Supplementary Material, File S2). Younger patients (Group 1) had a lower INTERMACS level compared with Group 2 (mean 1.7 vs 2.5; $P = 0.019$).

Outcomes

The mean age at the time of the implant was 13.8 years (range 5–18 years). Three children required a right VAD postoperatively: 1 in Group 1 (the patient died of an infection) and 2 in Group 2. The mean stay in the intensive care unit ranged from 3 days to 12 days with no differences between the groups (mean stay in the intensive care unit was 23.3 days vs 29.2 days). Thirty-seven (72%) patients were discharged either to their homes or to a rehabilitation facility. The mean support time was 8.4 months (8–1363 days). Forty-three (84%) children survived until transplant or recovery or are on support (Figs 1 and 2). Eight (16%) patients died while on support within the observed follow-up time: 3 from Group 1 (23%) and 5 from Group 2 (13%). The reasons for their deaths are presented in Table 4. At 12 months, 89% of the patients had received a transplant, were on support or had been successfully weaned from the device. Two late deaths occurred in patients who were on support for almost 2 years (716 days) or more (762 days). Right ventricular failure (1 in each group) and a cerebrovascular accident were the reasons for the late deaths.

Twenty-four (47%) children underwent transplants. The mean waiting time was 250 days (range 8–1033 days). An LVAD was explanted from only 1 patient due to myocardial recovery.

There were no differences between the groups regarding survival ($P = 0.21$; Fig. 2), transplant or recovery. In Group 1, 54% had transplants, whereas in the older age group, 55% had transplants within the observational period ($P = 0.29$).

Four (7%) children had pump thromboses: 1 in Group 1 and 3 in Group 2 (Table 5). However, there were no differences in the

Table 3: Patients' baseline characteristics at the time of implantation of the left ventricular assist device

	Entire study cohort	Group 1 <1.2 m^2	Group 2 ≥1.2 m^2	*P*-value
n	51	13	38	
Gender, male/female	27/24	6/7	21/17	0.40
Age (years), mean ± SD (range)	13.8 ± 3.5 (5–18)	9 ± 2.3 (5–13)	15.6 ± 1.8 (12–18)	<0.001
Body height (cm), mean ± SD (range)	163 ± 18.1 (113–193)	127.6 ± 12.7 (113–157)	171.4 ± 9.9 (153–193)	<0.001
Body weight (kg), mean ± SD (range)	51.8 ± 20.7 (17–99)	25.3 ± 5.3 (17–33)	60.6 ± 15.7 (35–99)	<0.001
Body surface area, mean ± SD (range)	1.5 ± 0.3 (0.7–2.2)	0.98 ± 0.1 (0.7–1.1)	1.6 ± 0.2 (1.2–2.2)	<0.001
EF at the time of admission (%), mean ± SD	19.3 ± 7.4	21 ± 11.4	18.7 ± 5.6	0.85
ECMO prior to VAD implant, *n* (%)	6 (12)	3 (23)	3 (8)	0.18
INTERMACS profile, mean ± SD (range)		1.7 ± 0.4 (1–2)	2.5 ± 1.1 (1–6)	0.019
Years of implant				
2009–2011	10	5	5	
2012–2014	24	4	20	
2014–2016	17	4	13	

EF: ejection fraction; ECMO: extracorporeal membrane oxygenation; VAD: ventricular assist device; INTERMACS: Interagency Registry for Mechanically Assisted Circulatory Support [22].

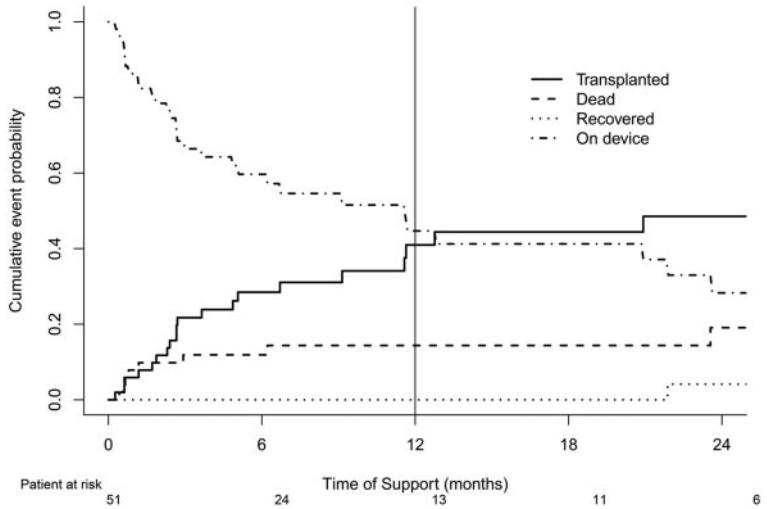

Figure 1: Competing outcome analysis of paediatric patients (EUROMACS) supported with continuous-flow left ventricular assist devices (1 January 2009–20 June 20 2016).

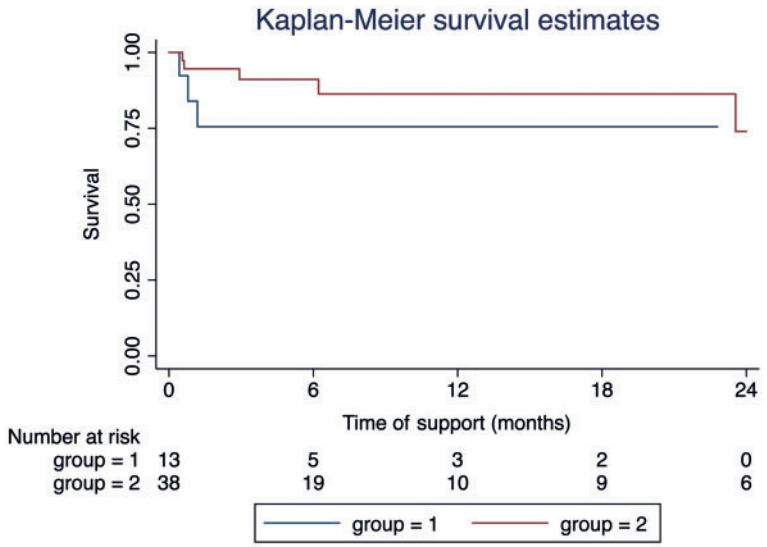

Figure 2: Survival for patients supported with centrifugal intracorporeal left ventricular assist devices with body surface area below (blue, Group 1) and above (red, Group 2) 1.2 m^2. Patients at risk are the patients on ventricular assist device support. Study end-points were death, transplantation or recovery. All patients were followed up to this event.

estimated flow rate between the groups (4.1 l/min vs 3.6 l/min; Table 5).

Anticoagulation

A majority of the patients ($n = 25$) were taking anticoagulation medication prior to implantation of the LVAD: 14 patients were taking heparin, 7 received antiplatelet treatment, 4 were taking oral anticoagulants and in 2 patients these details were unknown. Twenty-four patients did not receive anticoagulant agents prior to LVAD placement. Two patients in the whole cohort tested positive for heparin-induced thrombocytopenia prior to LVAD implantation. One of the patients died of cerebral stroke. After implantation of the LVAD, all of the patients received either heparin ($n = 49$) or an alternative ($n = 2$). Only a minority (38%) received additional antiplatelet therapy including aspirin, clopidogrel or dipyridamole. The target 'international normalized ratio' values ranged from 2 to 3.5. No significant differences were seen among the groups.

Cerebral strokes

Overall, 4 cerebral stroke events (0.1 events per patient-year) were observed in Group 2 without reaching significance ($P = 0.26$). Cerebral strokes occurred between 19 days and 524 days on support (mean = 244 days). All but 1 patient died of this event; 1 patient underwent a transplant. Cerebral strokes were preceded by a history of or a current event comprising pump thrombosis in 3 patients. None of the patients on extracorporeal membrane oxygenation prior to VAD implantation experienced a stroke. Among the early deaths after LVAD implantation, all patients except 1patient were extubated. In this 1 patient, there were no clear clinical signs of severe brain damage.

DISCUSSION

Ischaemic or haemorrhagic strokes are devastating complications for patients on VAD support. Different reports use disparate

definitions for these types of complications. INTERMACS and PediMACS use the term 'neurologic event rates', whereas a EUROMACS report uses the term 'neurologic dysfunction'. Other reports use the term 'cerebrovascular accidents'. One can assume that all reports refer to the same concept: significant neurological losses due to complications of the LVAD and/or anticoagulation impairing the daily activity of the patient and, therefore, his or her quality of life (QoL). For this reason, these rates are the absolute minimum that seems to be critical for counselling families prior to implantation and managing patients while on the device.

The seventh INTERMACS report mentions a neurological event rate of 20.4% in paediatric patients [9], which was confirmed by the PediMACS data with 26% cerebrovascular accidents [23]. There might be substantial differences in paediatric patients supported by VAD in terms of the concerned device, age, BSA, percentage of biventricular support and single ventricular physiology. Neurological dysfunctions including ischaemic stroke and haemorrhagic stroke were reported to be 3 times lower in patients with CFVADs compared to those in the pulsatile group [21]. In our analyses, we excluded not only pulsatile devices but also intracorporeal biventricular VADs. These analyses found an overall incidence of ischaemic or haemorrhagic stroke of 7% in patients younger than 19 years of age (0.1 events per patient-year). This incidence is comparable to the US data (PediMACS) reporting neurological dysfunction in 9 of 109 patients on CFVAD support [21].

Other trials investigating children on CFVADs described rates of cerebrovascular accidents to be between 0% and 16% [14–16, 20, 24–26]. None of the reports distinguished between implants according to manufacturing recommendations or off-label use in patients <1.2 m^2. This analysis found a cerebral stroke rate of 0.1 events per patient-year without finding any significant difference between the BSA groups. Interestingly, 75% of patients suffering from cerebral stroke had been treated previously for pump thrombosis (thrombolysis or device exchange). Although the cerebral stroke rates were low, the events led to death in three-fourths of the patients, thus becoming the most frequent cause of death (37%). The other fatal causes of death were multiorgan failure (25%), right ventricular failure (25%) and infections (12%). Compared with the PediMACS report (which focused on CF devices) [21], our cohort was comparable at 6 months (8% vs 9%) and 12 months (11% vs 12%). One of the main differences is the percentage of patients who received transplants: although 61% of the US patients had a transplant within the first 6 months, only 25% patients in Europe received a transplant during the same period. This difference indicates (as previously known) the lack of suitable organ donors in Europe and the longer support times in Europe. On the other hand, this difference also highlights the importance of QoL in these patients, and discharge is an important part of QoL. In this cohort, 72% of the patients were discharged (compared with PediMACS, where 45% were discharged). This outcome, in combination with a low cerebral stroke rate, justifies the increasing use of adult-approved CF devices in children.

A few other interesting findings emerged from in this study: although all the younger patients (Group 1) were taking inotropes and had a lower INTERMACS level prior to LVAD placement, only 80% of the patients in Group 2 received inotropes and also had a significantly higher INTERMACS level. One may speculate that physicians are more reluctant to implant intracorporeal LVADs, because placement and management in young children are more complex than in grown-up children. All fatalities in the younger patients occurred within 36 days of the LVAD procedure. The other interesting finding is that there were no differences in the estimated flow rates between the groups. One would expect lower flow rates for younger patients, but this was not the case. There were no differences concerning foetal right ventricular failure or the use of a right VAD between the groups. This point should be investigated further, because the authors provided no explanation for these topics in this project. On the other hand, the high flow rates might explain, in part, why the incidence of pump thrombosis and cerebral stroke did not differ between the groups and was comparable to that in adults.

Table 4: Causes of death

	Entire study cohort	Group 1 <1.2 m^2	Group 2 ≥1.2 m^2
All patients (*n*)	51	13	38
Cerebral strokes,[a] *n* (%)	3 (6)	0	3 (8)
Infections, *n* (%)	1 (2)	1 (8)	0
Right ventricular failure, *n* (%)	2 (4)	1 (8)	1 (3)
Multiorgan failure, *n* (%)	2 (4)	1 (8)	1 (3)

[a]Including ischaemic or haemorrhagic cerebral stroke.

Table 5: The outcomes for patients on a continuous-flow left ventricular assist device

	Entire study cohort	Group 1 <1.2 m^2	Group 2 ≥1.2 m^2	*P*-value
Death, *n* (%)	8 (15)	3 (23)	5 (13)	0.22
Heart transplant, *n* (%)	24 (47)	7 (54)	17 (55)	0.29
Postoperative RVAD, *n* (%)	3 (6)	1 (7)	2 (5)	0.72
Device explantation (due to myocardial recovery), *n* (%)	1 (2)	1 (7)	0	0.53
On support, *n* (%)	18 (35)	2 (15)	16 (42)	0.21
Support time, months, mean ± SD (range)	9.1 ± 44.2 (0.2–44.6)	7 ± 67.3 (0.4–22.7)	9.6 ± 55.1(0.2–44.6)	0.33
Pump thrombosis, *n* (%)	4 (7)	1 (7)	3 (8)	0.71
Flow rate (LVAD), (l/min), mean ± SD (range)	3.8 ± 0.2 (1.5–6.1)	4.1 ± 0.4 (2.5–6.1)	3.6 ± 0.2 (1.5–4.8)	0.64
ICU stay post-LVAD (days), mean ± SD	27.6 ± 0.5	23.2 ± 2.8	29.2 ± 6.9	0.38

[a]Defined as pump exchange or thrombolysis treatment.
LVAD: left ventricular assist device; ICU: intensive care unit; RVAD: right ventricular assist device.

Limitations

This study has several limitations inherent to retrospective data collection, and we must mention that not all European centres report their data to EUROMACS. The volume in European centres is in most cases smaller than that in US centres, and it is clear that all of the centres experienced a 'learning curve'. The volume handled by the different centres and the starting point of CF LVAD implantation may be seen in Supplementary Material, File S3.

The biggest drawback is that the event rate was too small to conduct a proper risk factor or multivariate analysis. As in all registries, events may be under-reported. The report could be biased by the fact that not all patients from the participating centres were included, and some centres may not have sent their reports at all due to unfavourable results. The EUROMACS Registry tries to prevent this by applying several quality control methods. The definition of cerebral strokes covers a wide range of symptoms and, because this is a database analysis, it is possible that we could have missed some mild symptoms without a relevant impact on QoL.

The cut-off point of 1.2 m^2 for the BSA was chosen because of the approval of 1 device, but this might differ for other devices. Furthermore, the number of young children (BSA <1.2 m^2) was low ($n = 13$). To rule out that deaths and neurological events cluster around a low BSA, we stratified the results according to the BSA (see Supplementary Material, File S4). Despite these limitations, this is the first report of children supported with CF LVADs that has emerged from the EUROMACS database, thereby adding further information to that already published concerning the US cohort (PediMACS).

CONCLUSION

The incidence of cerebral strokes in children with intracorporeal VADs (0.1 per patient-year) seems to be low irrespective of whether the patients have a BSA above or below 1.2 m^2.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

Conflict of interest: none declared.

REFERENCES

[1] Fraser CD Jr, Jaquiss RD, Rosenthal DN, Hump L. T, Canter CE, Blackstone EH. Prospective trial of a pediatric ventricular assist device. N Engl J Med 2012;367:532–41.

[2] Morales DL, Almond CS, Jaquiss RD, Rosenthal DN, Naftel DC, Massicotte MP. Bridging children of all sizes to cardiac transplantation: the initial multicenter North American experience with the Berlin Heart EXCOR ventricular assist device. J Heart Lung Transplant 2011;30:1–8.

[3] Jeewa A, Manlhiot C, McCrindle BW, Van Arsdell G, Humpl T, Dipchand AI. Outcomes with ventricular assist device versus extracorporeal membrane oxygenation as a bridge to pediatric heart transplantation. Artif Organs 2010;34:1087–91.

[4] Schweiger M, Schrempf J, Sereinigg M, Prenner G, Tscheliessnigg KH, Wasler A. Complication Profile of the Berlin Heart EXCOR Biventricular Support in Children. Artif Organs 2013;37:730–5.

[5] Byrnes JW, Prodhan P, Williams BA, Schmitz ML, Moss MM, Dyamenahalli U. Incremental reduction in the incidence of stroke in children supported with the Berlin EXCOR ventricular assist device. Ann Thorac Surg 2013;96:1727–33.

[6] Fan Y, Weng Y-G, Xiao Y-B, Huebler M, Franz N, Potapov E *et al*. Outcomes of ventricular assist device support in young patients with small body surface area. Eur J Cardiothorac Surg 2011;39:699–704.

[7] Warnecke H, Berdjis F, Hennig E, Lange P, Schmitt D, Hummel M. Mechanical left ventricular support as a bridge to cardiac transplantation in childhood. Eur J Cardiothorac Surg 1991;5:330–3.

[8] de By TM, Mohacsi P, Gummert J, Bushnaq H, Krabatsch T, Gustafsson F *et al*. The European Registry for Patients with Mechanical Circulatory Support (EUROMACS): first annual report. Eur J Cardiothorac Surg 2015; 47:770–6; discussion 776–7.

[9] Kirklin JK, Naftel DC, Pagani FD, Kormos RL, Stevenson LW, Blume ED *et al*. Seventh INTERMACS annual report: 15,000 patients and counting. J Heart Lung Transplant 2015;34:1495–504.

[10] Slaughter MS, Rogers JG, Milano CA, Conte JV, Feldman D, Sun B *et al*. Advanced heart failure treated with continuous-flow left ventricular assist device. N Engl J Med 2009;361:2241–51.

[11] Kirklin JK, Naftel DC, Kromos RL, Stenenson LW, Pagani FD, Miller MA *et al*. Fifth INTERMACS annual report: risk factor analysis from more than 6, 000 mechanical circulatory support patients. J Heart Lung Transplant 2013;32:141–56.

[12] Fraser CD, Carberry KE, Owens WR, Arrington KA, Morales DLS, Heinle JS *et al*. Preliminary experience with the MicroMed DeBakey pediatric ventricular assist device. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu 2006;9:109–14.

[13] Owens WR, Bryant Iii R, Dreyer WJ, Price JF, Morales DLS. Initial clinical experience with the HeartMate II ventricular assist system in a pediatric institution. Artif Organs 2010;34:600–3.

[14] Cabrera AG, Sundareswaran KS, Samayoa AX, Jeewa A, Dean McKenzie E, Rossano JW *et al*. Outcomes of pediatric patients supported by the HeartMate II left ventricular assist device in the United States. J Heart Lung Transplant 2013;32:1107–13.

[15] Sparks J, Epstein D, Baltagi S, Mehegan ME, Simpson KE, Canter CE *et al*. Continuous flow device support in children using the HeartWare HVAD: 1000 days of lessons learned from a single center experience. ASAIO J 2015;61:569–73.

[16] Miera O, Potapov EV, Redlin M, Stepanenko A, Berger F, Hetzer R *et al*. First experiences with the HeartWare ventricular assist system in children. Ann Thorac Surg 2011;91:1256–60.

[17] Schweiger M, Dave H, Lemme F, Cavigelli-Brunner A, Romanchenkoe O, Heineking B *et al*. Acute chemotherapy-induced cardiomyopathy treated with intracorporeal left ventricular assist device in an 8-year-old child. ASAIO J 2013;59:520–2.

[18] Padalino MA, Ohye RG, Chang AC, Gajarski RJ, Bove EL, Devaney EJ. Bridge to transplant using the MicroMed DeBakey ventricular assist device in a child with idiopathic dilated cardiomyopathy. Ann Thorac Surg 2006;81:1118–21.

[19] Morales DLS, DiBardino DJ, McKenzie ED, Heinle JS, Chang AC, Loebe M *et al*. Lessons learned from the first application of the DeBakey VAD Child: an intracorporeal ventricular assist device for children. J Heart Lung Transplant 2005;24:331–7.

[20] Schweiger M, Vanderpluym C, Jeewa A, Canter CE, Jansz P, Parrino PE *et al*. Outpatient management of intra-corporeal left ventricular assist device system in children: a multi-center experience. Am J Transplant 2015;15:453–60.

[21] Rossano JW, Lorts A, VanderPluym CJ, Jeewa A, Guleserian KJ, Bleiweis MS *et al*. Outcomes of pediatric patients supported with continuous-flow ventricular assist devices: A report from the Pediatric Interagency Registry for Mechanical Circulatory Support (PediMACS). J Heart Lung Transplant 2016;35:585–90.

[22] Kirklin JK, Naftel DC, Stevenson LW, Kormos RL, Pagani FD, Miller MA *et al*. INTERMACS database for durable devices for circulatory support: first annual report. J Heart Lung Transplant 2008;27:1065–72.

[23] Blume ED, Rosenthal DN, Rossano JW, Baldwin JT, Eghtesady P, Morales DLS *et al*. A., Outcomes of children implanted with ventricular assist devices in the United States: First analysis of the Pediatric Interagency Registry for Mechanical Circulatory Support (PediMACS). J Heart Lung Transplant 2016;35:578–84.,

[24] Chen S, Lin A, Liu E, Gowan M, May LJ *et al*. Outpatient outcomes of pediatric patients with left ventricular assist devices. ASAIO J 2016;62:163–8.

[25] Padalino MA, Bottio T, Tarzia V, Bortolussi G, Cerutti A, Vida VL *et al*. HeartWare ventricular assist device as bridge to transplant in children and adolescents. Artif Organs 2014;38:418–22.

[26] Miera O, Kirk R, Buchholz H, Schmitt KR, VanderPluym C, Rebeyka IM *et al*. A multicenter study of the HeartWare ventricular assist device in small children. J Heart Lung Transplant 2016;35:679–81.