European Journal of Cardio-Thoracic Surgery 2024, 66(2), ezae276
https://doi.org/10.1093/ejcts/ezae276 Advance Access publication 19 July 2024

ORIGINAL ARTICLE

Cite this article as: Rohde S, van Puyvelde J, Veen KM, Schweiger M, Biermann D, Amodeo A *et al.* The European Registry for Patients with Mechanical Circulatory Support (EUROMACS): fourth Paediatric EUROMACS (Paedi-EUROMACS) report. Eur J Cardiothorac Surg 2024; doi:10.1093/ejcts/ezae276.

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

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Received 31 January 2024; received in revised form 15 June 2024; accepted 18 July 2024

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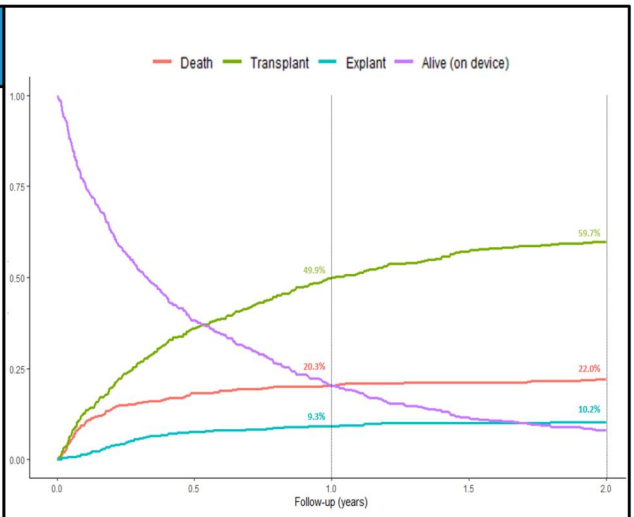
Fourth Paediatric EUROMACS (Paedi-EUROMACS) report

Summary

Between January 2001 and June 2022, 590 primary implantations were included form 29 centers in 15 different countries. After 2 years of VAD support, 22.0% deceased, 59.7% could be transplanted and 10.2% recovered. Patients with CHD have higher mortality rates and lower transplantation rates compared to paediatric non-CHD patients (30.8% vs. 20.4%; 52.7% vs. 60.8% at 2 year). Thromboembolic adverse events are higher in pulsatile supported patients



CHD = congenital heart disease; VAD = ventricular assist device

Abstract

OBJECTIVES: The use of ventricular assist devices (VADs) in children is increasing. However, absolute numbers in individual centres and countries remain small. Collaborative efforts such as the Paedi-European Registry for Patients with Mechanical Circulatory Support (EUROMACS) are therefore essential for combining international experience with paediatric VADs. Our goal was to present the results from the fourth Paedi-EUROMACS report.

METHODS: All paediatric (<19 years) patients from the EUROMACS database supported by a VAD were included. Patients were stratified into a congenital heart disease (CHD) group and a group with a non-congenital aetiology. End points included mortality, a transplant and recovery. Cox proportional hazard models were used to explore associated factors for mortality, cerebrovascular accident and pump thrombosis.

RESULTS: A total of 590 primary implants were included. The congenital group was significantly younger (2.5 vs 8.0 years, respectively, $P < 0.001$) and was more commonly supported by a pulsatile flow device (73.5% vs 59.9%, $P < 0.001$). Mortality was significantly higher in the congenital group (30.8% vs 20.4%, $P = 0.009$) than in the non-congenital group. However, in multivariable analyses, CHD was not significantly associated with mortality [hazard ratio (HR) 1.285; confidence interval (CI) 0.8111–2.036, $P = 0.740$]. Pump thrombosis was the most frequently reported adverse event (377 events in 132 patients; 0.925 events per patient-year) and was significantly associated with body surface area (HR 0.524, CI 0.333–0.823, $P = 0.005$), CHD (HR 1.641, CI 1.054–2.555, $P = 0.028$) and pulsatile flow support (HR 2.345, CI 1.406–3.910, $P = 0.001$) in multivariable analyses.

CONCLUSIONS: This fourth Paedi-EUROMACS report highlights the increasing use of paediatric VADs. The patient populations with congenital and non-congenital aetiologies exhibit distinct characteristics and clinical outcomes.

Keywords: Mechanical circulatory support • Ventricular assist device • Paediatric • Transplantation • EUROMACS

ABBREVIATIONS

BHE	Berlin Heart EXCOR
BSA	body surface area
CHD	congenital heart disease
CVA	cerebrovascular accident
DCM	dilated cardiomyopathy
ECMO	extracorporeal membrane oxygenation
EUROMACS	European Registry for Patients with Mechanical Circulatory Support database
HR	hazard ratio
HM3	HeartMate 3
HVAD	HeartWare ventricular assist device
INTERMACS	Interagency Registry for Mechanically Assisted Circulatory Support
VAD	ventricular assist device

INTRODUCTION

The European Registry for Patients with Mechanical Circulatory Support (EUROMACS) was founded in 2009, and it published its first report in 2015 [1]. In the years that followed, more hospitals have joined and the number of patients included in this database has increased dramatically [2]. Rapid changes in technology call for joint efforts like this to provide a platform for systematic, rigorous scientific research [3]. EUROMACS facilitates access to a large data set for individual research questions and enables research groups to study many facets of patients undergoing this treatment modality.

Mechanical circulatory support therapy in children, especially support by a ventricular assist device (VAD), is less frequent than in adults with terminal heart failure, and there is a paucity of child-specific device choices primarily due to commercial imperatives [4]. In this population, the EUROMACS registry is particularly valuable because it aggregates a substantial number of patients, which allows researchers to extract insights that are directly applicable to everyday clinical practice. Therefore, the Paediatric EUROMACS (Paedi-EUROMACS) subcommittee was founded in 2019 [5].

We present herein the fourth annual report of the Paedi-EUROMACS. The report provides an overview of the current experiences with paediatric mechanical circulatory support within the EUROMACS framework.

METHODS

Database

The EUROMACS database, maintained by the European Association for Cardio-Thoracic Surgery, currently includes paediatric patients from 43 centres in 19 different countries. Data sharing with the EUROMACS registry is voluntary. Per patient, around 550 baseline variables can be enrolled with an additional 450 variables per follow-up event per patient. The quality of the data in the EUROMACS database is monitored with different methods including cross-referencing and on-site audits. Data in the registry undergo random one-on-one verification with the data in the hospitals' patient files. Adverse events are reported according to the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) definitions [6].

Ethical statement

All individual hospitals received approval from their medical/research ethics committee in accordance with *European Journal of Cardio-Thoracic Surgery* policy.

Inclusion criteria. For this report, all paediatric (<19 years) patients registered in the EUROMACS database who were supported by a durable left, biventricular or single ventricular assist device between January 2001 and June 2022 were included. Children supported by a right ventricular assist device alone were not included. Only index implants were analysed (Fig. 1).

Primary and secondary outcomes

The primary outcome of this study was the competing outcomes mortality, cardiac transplant and explants due to myocardial recovery.

The secondary outcomes included adverse events like pump thrombosis, infection, stroke, bleeding, cardiac arrhythmia, right ventricular failure, respiratory failure, renal dysfunction and thromboembolism.

Statistical analyses

Patients were stratified by aetiology. Continuous data are presented as median (interquartile range) since they did not show a Gaussian distribution, and categorical data are presented as frequencies (percentage). Complete case analyses were performed. Percentages of missing data are presented in Supplementary Material, Table S1. The modified Clark C metric is used to calculate follow-up completeness. Follow-up time is described by median duration of support. The Mann–Whitney test was used

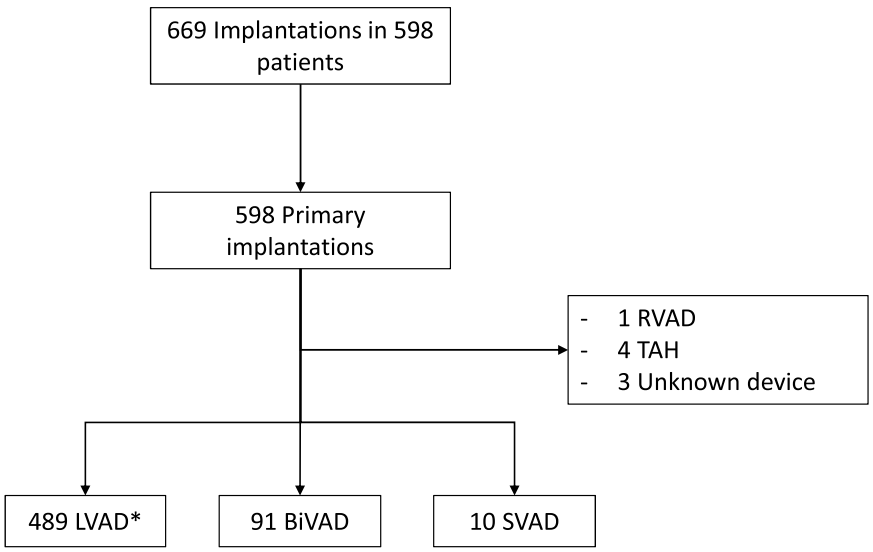


Figure 1: Flow chart of included patients.

to compare continuous variables. The χ^2 test or the Fisher exact test (<10 observations per cell) was used to compare categorical variables. The Aalen Johanssen estimator was used to estimate actual probability of death, recovery or a transplant in the different aetiology groups. Gray's test was used to compare curves [7]. Adverse event rates and their 95% confidence intervals were calculated [8]. Potential determinants of mortality, cerebral vascular accident (CVA), pump thrombosis, major bleeding and infection were explored with multivariable Cox proportional hazard models, to derive cause-specific hazard ratios (HR). Determinants were chosen based on clinical relevance, and no predictor selection procedures were performed. Proportional hazard assumption was tested using the Schoenfeld residuals *F* test. All *P*-values were above 0.05, except for mortality with $P = 0.045$. Based on visual inspection of the residuals, no major deviations were noted, and no extra measures for relaxing the proportional hazard assumption were taken. All analyses were performed in International Business Machines Corporation Statistical Package for the Social Sciences (IBM SPSS, Armonk, NY, USA) statistics (Version 24) or R (Version 4.0.3) with the packages "Survival", "cmprsk" and "gpreg".

RESULTS

By August 2023, a total of 590 primary implants in children <19 years old were included in the EUROMACS database (Fig. 1). This number is an increase of 120 implants compared to the previous report. Over half of the patients were above the age of 6, with younger patients being more likely to receive support from a paracorporeal pulsatile flow VAD, whereas older patients were more likely to be supported by an implantable continuous flow VAD. The Berlin Heart EXCOR (BHE) was the most commonly used device for paracorporeal pulsatile flow VADs, whereas the HeartWare ventricular assist device (HVAD) was the preferred choice for implantable continuous flow VADs. The proportion of HVADs decreased from 27.1% in the previous report to 20.3%. Conversely, the percentage of BHE increased from 53.4% to 59%, and the percentage of HeartMate 3 (HM3)-supported patients increased from 4.1% to 5.4%. The median age for HM3 implants in our cohort remained at 16 years, with a median weight of 52.8 kg, whereas the median age for the HVAD implant was 13 years, with a median weight of 43 kg. The smallest child in our study who received a HM3 was a 10-year-old with a body surface area (BSA) of 0.91 m^2 and a weight of 23 kg (ongoing support at the last follow-up). Dilated cardiomyopathy is the most prevalent cause of heart failure in VAD-supported children, accounting for 74% of cases. Within this group, 36.6% have idiopathic dilated cardiomyopathy (DCM), whereas 16% need mechanical support for severe myocarditis. A total of 17% of the patients have an underlying congenital heart disease (CHD).

Patients were divided into 2 groups: children with a primary diagnosis of a CHD (CHD group, $n = 98$) and children with other primary diagnoses (non-CHD group, $n = 479$) such as cardiomyopathy or myocarditis. Thirteen children could not be classified into a group (e.g. in case of "valvular heart disease"). The CHD group was significantly younger (2.5 vs 8.0 years, $P < 0.001$) and were more frequently supported by a pulsatile flow device (73.5% vs 59.9%, $P < 0.001$). They had more often an INTERMACS profile of I or II (33.7–54.1% vs 23.8–49.7%, $P = 0.035$). Previous intubation, dialysis, extracorporeal membrane oxygenation (ECMO) support and cardiac surgery were more frequent in this subgroup (54.1% vs 37.4%, $P = 0.005$; 9.2% vs 2.1%, $P = 0.001$; 34.0% vs 20.9%, $P = 0.012$; 53.1% vs 6.9%, $P < 0.001$). Furthermore, time of implant since first diagnosis and mode of support differed significantly ($P < 0.001$) (Table 1). In the non-CHD group, the most frequent diagnosis was (idiopathic) DCM (Fig. 2). In the CHD groups, various diagnoses existed, with 16% of the children having hypoplastic left heart/single ventricle (Fig. 2). Figure 3 shows the ratio between CHD and non-CHD VAD implants over the past decade. In Fig. 4, the ratio of CHD versus non-CHD supported children is visualized per country. In countries such as Spain and Hungary, more than 30% of the VAD-supported children had a primary diagnosis of a CHD. In contrast, countries as the Netherlands, Italy and the Czech Republic had a far lower percentage of patients with CHD in their population (0–10%).

Follow-up

The median duration of support was 116.0 (IQR 37.0–298.5) days in the overall group (Table 1). For the patients who received transplants, the median duration of support was 136.0 (IQR 50.05–311.5) days. At the end of follow-up (June 2022), 16 children were still on HVAD support. Follow-up completeness was 85.04%.

Clinical outcomes

At the 2-year follow-up, the probability of a transplant was 59.7%, and the probability of recovery was 10.2% in all the paediatric patients included. Mortality probability after 2 years of VAD support in the overall paediatric VAD population was 22.0%. In the second year, mortality and recovery probabilities barely increased compared to the probability of a transplant (Fig. 4). In the CHD group, the probability of a transplant at the 2-year follow-up was 52.7%; the recovery probability, 14.0%; and the probability of death was 30.8%. In the non-CHD group, 60.8% received transplants (Gray test: $P = 0.100$) and 9.7% recovered after 2 years (Gray test: $P = 0.202$). The probability of death was significantly higher in the CHD group compared to non-CHD group (20.4% vs 30.8% at 2 years, Gray test: $P = 0.009$; Fig. 5). However, with the multivariable Cox proportional hazard regression models, CHD was not significantly associated with death (HR 1.285, CI 0.8111–2.036, $P = 0.740$). A worse INTERMACS profile (I–II vs ≥III, HR 0.582, CI 0.345–0.981, $P = 0.042$) and previous support with ECMO (HR 1.804, CI 1.216–2.675, $P = 0.003$) were significantly associated with deaths in the multivariable analysis (Table 2). CVA (in 53 of the 132 deaths) and multiorgan failure (33 of the 132 deaths) were the most frequently reported causes of death (Table 3).

Adverse events

Pump thrombosis was the most frequently reported adverse event (377 events in 132 patients; 0.925 events per patient-year). Infection (192 events in 107 patients; 0.417 events per patient-year) and CVA (154 events in 126 patients; 0.378 events per patient-year) were frequent as well (Table 4). A total of 107/377 (28.4%) of the pump thrombosis events occurred within 30 days and 197/377 within 90 days (52.3%); 63/154 (40.9%) strokes occurred within 30 days and 108/154 (70.1%), within 90 days.

Table 1: Baseline characteristics of congenital heart disease versus non- congenital heart disease patients

	All ($n = 590$)*	CHD ($n = 98$)	Non-CHD ($n = 479$)	*P*-value
Male sex, n (%)	327 (55.4)	55 (56.1)	262 (54.7)	0.796
Age (years), median (IQR)	6.5 (1.0–13.0)	2.5 (0.6–5.0)	8.0 (1.0–14.0)	<0.001
<1 y, n (%)	123 (20.8)	27 (27.6)	95 (19.8)	
1–5 y, n (%)	158 (26.8)	48 (49.0)	107 (22.3)	
6–10 y, n (%)	94 (15.9)	10 (10.2)	82 (17.1)	
11–19 y, n (%)	215 (36.4)	13 (13.3)	195 (40.7)	
BSA (m^2), median (IQR)	0.9 (0.4–1.5)	0.6 (0.4–1.2)	0.9 (0.5–1.5)	0.012
Weight (kg), median (IQR)	19.0 (9.0–44.0)	11.6 (6.6–19.0)	22.0 (9.4–45.1)	<0.001
<5 kg, n (%)	40 (6.8)	11 (11.2)	29 (6.1)	
5–9 kg, n (%)	125 (21.2)	32 (32.7)	91 (19.0)	
10–20 kg, n (%)	138 (23.4)	33 (33.7)	102 (21.3)	
21–40 kg, n (%)	117 (19.8)	12 (12.2)	102 (21.3)	
41–70 kg, n (%)	119 (20.2)	7 (7.1)	110 (23.0)	
>70 kg, n (%)	34 (5.8)	0	31 (6.5)	
Unspecified**, n (%)	17 (2.9)	3 (3.1)	14 (2.9)	
INTERMACS classification				0.035
I, n (%)	149 (25.3)	33 (33.7)	114 (23.8)	
II, n (%)	296 (50.2)	53 (54.1)	238 (49.7)	
III, n (%)	95 (16.1)	7 (7.1)	86 (18.0)	
IV, n (%)	23 (3.9)	2 (2.0)	21 (4.4)	
V–VII, n (%)	15 (2.5)	2 (2.0)	10 (2.1)	
Unknown**, n (%)	12 (2.0)	1 (1.0)	10 (2.1)	
Time since first diagnosis				<0.001
<1 month, n (%)	187 (31.7)	13 (13.3)	172 (35.9)	
1 month–1 year, n (%)	158 (26.8)	22 (22.4)	135 (28.2)	
1–2 years, n (%)	49 (8.3)	6 (6.1)	43 (9.0)	
>2 years, n (%)	136 (23.1)	37 (37.8)	93 (19.4)	
Unknown**, n (%)	60 (10.2)	20 (20.4)	7 (1.5)	
Number of inotropes				0.084
0	60 (10.2)	9 (9.2)	48 (10.0)	
1–2	337 (57.1)	50 (51.0)	283 (59.1)	
3–4	111 (18.8)	27 (27.6)	81 (16.9)	
>4	4 (0.7)	0	4 (0.8)	
Unknown**	78 (13.2)	12 (12.2)	63 (13.2)	
Previous intubation, n (%)	238 (40.3)	53 (54.1)	179 (37.4)	0.005
Previous dialysis, n (%)	19 (3.2)	9 (9.2)	10 (2.1)	0.001
Previous ECMO, n (%)	138 (23.4)	34 (34.7)	100 (20.9)	0.012
Previous IABP, n (%)	4 (0.7)	0	4 (0.8)	0.509
Previous cardiac surgery, n (%)	88 (14.9)	52 (53.1)	33 (6.9)	<0.001
Previous cardiac arrest, n (%)	73 (12.4)	18 (18.4)	55 (11.5)	0.174
Device strategy				0.879
Possible bridge to transplant, n (%)	156 (26.4)	26 (26.5)	128 (26.7)	
Bridge to transplant (currently listed), n (%)	371 (62.9)	60 (61.2)	302 (63.0)	
Bridge to recovery, n (%)	42 (7.1)	8 (8.2)	33 (6.9)	
Rescue therapy, n (%)	17 (2.9)	4 (4.1)	12 (2.5)	
Destination therapy, n (%)	3 (0.5)	0	3 (0.6)	
Unknown, n (%)	1 (0.2)	0	1 (0.2)	
Type of support				<0.001
LVAD, n (%)	454 (76.9)	65 (66.3)	377 (78.7)	
BiVAD, n (%)	91 (15.4)	14 (14.3)	76 (15.9)	
LVAD with secondary placed RVAD, n (%)	35 (4.9)	9 (9.2)	26 (5.4)	
SVAD, n (%)	10 (1.7)	10 (10.2)	0	
Mode of support				<0.001
Pulsatile flow	367 (62.2)	72 (73.5)	287 (59.9)	
Berlin Heart EXCOR, n (%)	348 (59.0)	72 (73.5)	270 (56.4)	
Thoratec PVAD, n (%)	5 (0.8)	0	4 (0.8)	
Continuous flow	215 (36.4)	18 (18.4)	192 (40.1)	
Heartmate II, n (%)	12 (2.0)	1 (1.0)	11 (2.3)	
Heartmate 3, n (%)	32 (5.4)	2 (2.0)	28 (5.8)	
HeartWare, n (%)	120 (20.3)	7 (7.1)	109 (22.8)	
HeartAssist 5, n (%)	2 (0.3)	0	2 (0.4)	
Jarvik 2000, n (%)	12 (2.0)	0	12 (2.5)	
Berlin Heart Incor, n (%)	5 (0.8)	0	5 (1.0)	
Unknown**, n (%)	8 (1.4)	8 (8.2)	0	
Median time of support, days (IQR)	116.0 (37.0–298.5)	79.0 (22.0–275.0)	121.0 (39.0–299.0)	0.057

*7 unknown primary diagnosis; 6 valvular heart disease.

**The unknown/unspecified groups were not included in the analyses.

BiVAD: biventricular assist device; BSA: body surface area; CHD: congenital heart disease; ECMO: extracorporeal membrane oxygenation; IABP: intra-aortic balloon pump; INTERMACS: Interagency Registry for Mechanically Assisted Circulatory Support; IQR: interquartile range; LVAD: left ventricular assist device; PVAD: percutaneous ventricular assist device; RVAD: right ventricular assist device; SVAD: single ventricular assist device.

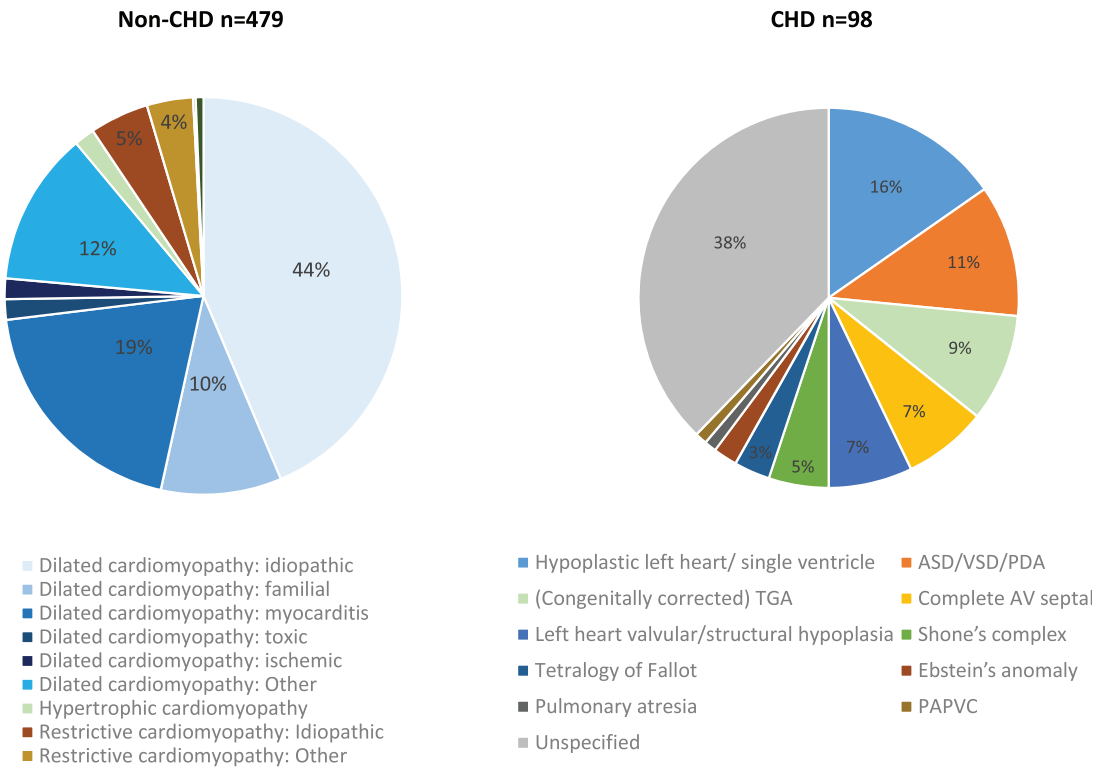


Figure 2: Aetiology specified.

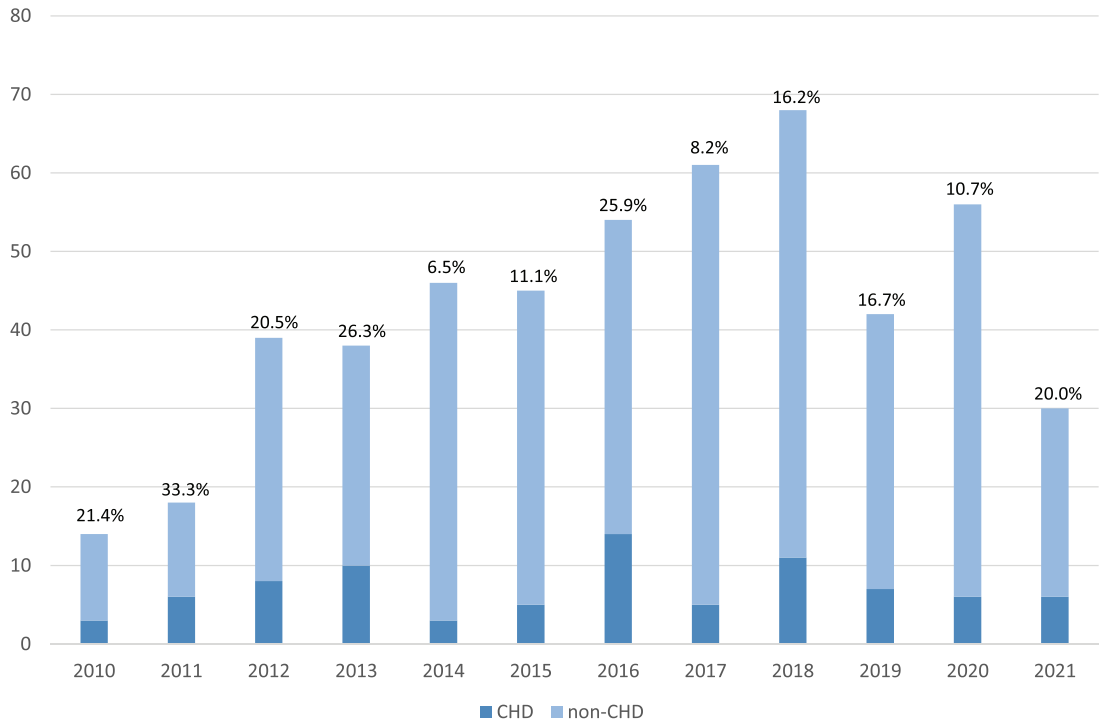


Figure 3: Frequency of ventricular assist device implants in congenital heart disease versus non-congenital heart disease patients over time stratified according to aetiology.

Pump thrombosis (2.253 vs 0.788 events per patient-year; $P < 0.001$), pump malfunction (0.386 vs 0.156 events per patient-year; $P < 0.001$), infection (0.901 vs 0.603 events per patient-year; $P = 0.017$) and arterial non-central nervous system thromboembolism (0.086 vs 0.020 events per patient-year; $P = 0.012$), were significantly more frequent in the CHD group, whereas cardiac arrhythmias happened significantly more often in the non-CHD group (0 vs 0.217 events per patient-year;

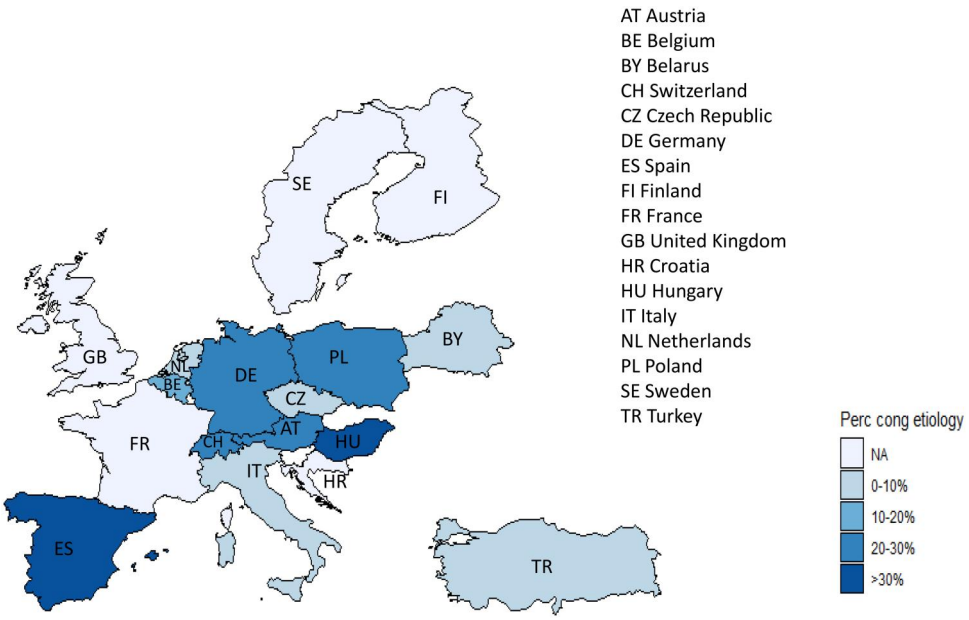


Figure 4: Percentage of ventricular assist device implants in congenital heart disease versus non- congenital heart disease patients per country.

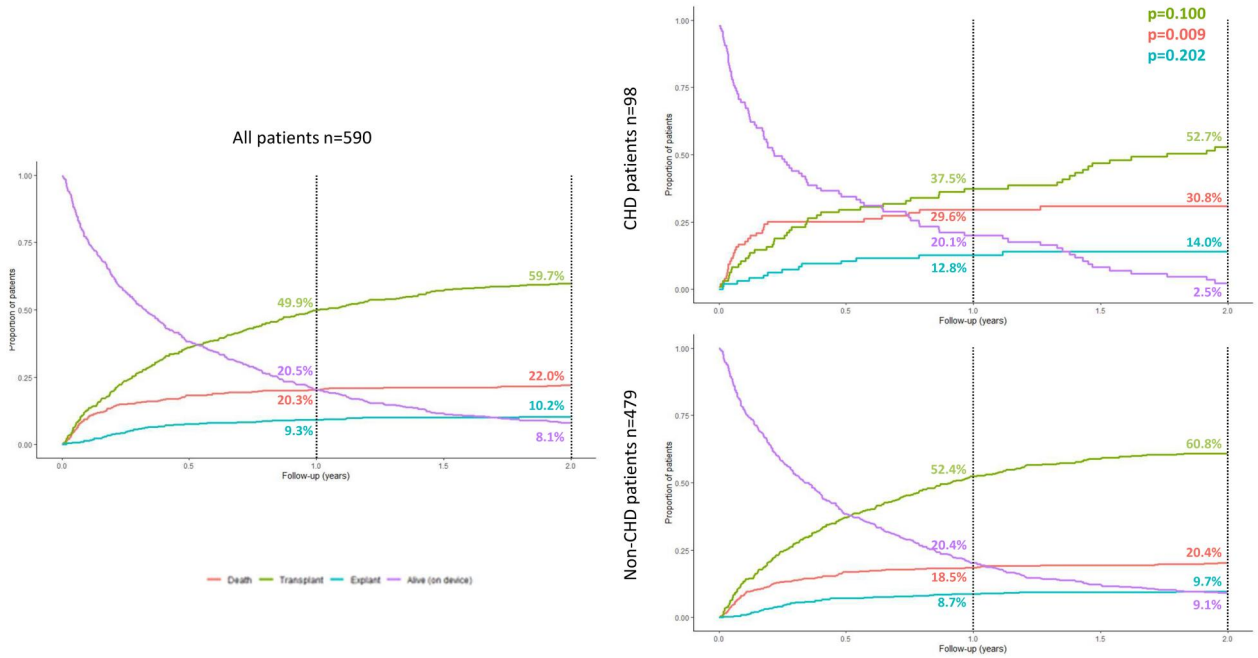


Figure 5: Competing outcomes of congenital heart disease versus non-congenital heart disease patients.

$P = 0.002$) (Table 4). In multivariable analyses, aetiology (CHD vs non-CHD) was significantly associated with pump thrombosis (HR 1.641, CI 1.054–2.555, $P = 0.028$) but not with CVA (HR 0.740, CI 0.416–1.318, $P = 0.307$; Table 2). BSA was significantly associated with CVA and pump thrombosis (HR 0.486, CI 0.313–0.754, $P = 0.001$ and HR 0.524, CI 0.333–0.823, $P = 0.005$, respectively).

Adverse event rates also differed per mode of support. Pump thrombosis (1.822 vs 0.289 events per patient year; $P < 0.001$), device malfunction other than pump thrombosis (0.366 vs 0.042 events per patient year; $P < 0.001$), CVA (0.607 vs 0.212 events per patient year; $P < 0.001$) and bleeding (0.348 vs 0.221 events per patient year; $P = 0.016$) were more commonly observed in patients supported by a pulsatile flow device rather than a continuous flow device (Table 5). Furthermore, pulsatile flow support was significantly associated with pump thrombosis in multivariable analyses (HR 2.345, CI 1.406–3.910, $P = 0.001$) but not with stroke (HR 1.190, CI 0.733–1.931, $P = 0.483$; Table 2). Cardiac arrhythmias occurred significantly more often in the continuous flow-supported patients (0.272 vs 0.065 events per patient year; $P < 0.001$; Table 5).

Previous ECMO support was significantly associated with major bleeding (HR 2.043, CI 1.244–3.355) in multivariable analyses but not with stroke or pump thrombosis (Table 2).

Table 2: Multivariable Cox proportional hazard regression model: Associated factors for mortality, cerebral vascular accident, pump thrombosis, major bleeding and infection

	Mortality			CVA*			Pump thrombosis		
	HR	CI	*P*	HR	CI	*P*	HR	CI	*P*
BSA	0.994	0.931–1.061	0.858	0.486	0.313–0.754	0.001	0.524	0.333–0.823	0.005
CHD vs non-CHD	1.285	0.811–2.036	0.285	0.789	0.460–1.353	0.389	1.641	1.054–2.555	0.028
Pulsatile vs continuous flow	1.379	0.916–2.078	0.124	1.190	0.733–1.931	0.483	2.345	1.406–3.910	0.001
INTERMACS profile (I–II vs ≥III)	0.582	0.345–0.981	0.042	1.275	0.801–2.030	0.305	1.081	0.700–1.667	0.727
Previous ECMO	1.804	1.216–2.675	0.003	0.897	0.569–1.413	0.639	0.767	0.484–1.217	0.261

	Major bleeding			Infection		
	HR	CI	*P*	HR	CI	*P*
BSA	0.906	0.520–1.577	0.726	0.637	0.382–1.062	0.084
CHD vs non-CHD	1.232	0.660–2.297	0.512	1.315	0.761–2.272	0.327
Pulsatile vs continuous flow	0.665	0.364–1.215	0.185	0.602	0.350–1.035	0.067
INTERMACS profile (I–II vs ≥III)	1.902	0.948–3.816	0.070	0.939	0.584–1.510	0.795
Previous ECMO	2.043	1.244–3.355	0.005	1.546	0.978–2.446	0.062

*All types (ischaemic, haemorrhagic and unspecified) were included.

BSA: body surface area; CHD: congenital heart disease; CI: confidence interval; CVA: cerebrovascular accident; ECMO: extracorporeal membrane oxygenation; HR: hazard ratio; INTERMACS: Interagency Registry for Mechanically Assisted Circulatory Support.

Table 3: Causes of death

	All (*n* = 132)*	CHD (*n* = 30)	Non-CHD (*n* = 100)
CVA, n (%)	53 (40.2)	5 (16.7)	46 (46)
Ischaemic	4		
Haemorrhagic	18		
Unspecified	31		
Infectious, n (%)	19 (14.4)	8 (26.7)	11 (11)
Bleeding, n (%)	9 (6.8)	4 (13.3)	5 (5)
Thoracic	5		
Lower gastrointestinal	1		
Unspecified	3		
Multiorgan failure (without bleeding or infection specified as cause), n (%)	33 (25.0)	8 (26.7)	25 (25)
Device malfunction, n (%)	2 (1.5)	0	2 (2)
Unspecified, n (%)	16 (12.1)	5 (16.7)	11 (11)

*Two patients with unspecified diagnosis died, both of CVA.

CHD: congenital heart disease; CVA: cerebrovascular accident.

DISCUSSION

This fourth Paedi-EUROMACS report builds on the previous reports and focuses on the outcomes of non-CHD and CHD patients in more detail. The number of registered primary paediatric implants reported in this report increased compared to the number in the previous report [2]. This trend was consistent with the findings of the sixth North American Pedimacs report, which reported an increase of 98 primary implants for a total of 1109 primary paediatric implants [9]. This result represented a total of more than 200 cases a year across both continents, indicating the growing utility of paediatric VADs across both registries.

Mode of support

The discrepancy in the use of paracorporeal pulsatile flow devices (primarily BHE) versus implantable continuous flow devices (historically mostly HVAD) across different ages stems mainly from limitations in device selection due to patient size. The smaller HVAD offered a viable intracorporeal option for smaller or younger children compared to the larger HM3. However, following the discontinuation of the HVAD due to higher adverse event rates compared to HM3 in adults [10], it is anticipated that most young children who previously would have received an HVAD will now be fitted with a BHE, whereas older children are more likely to receive an HM3 [11]. Future annual reports are expected to reveal a new balance in device choice. As for the data used for the current report, which included children already established on support, the proportion on HVAD support decreased, and the percentage of BHE- and HM3-supported patients increased. As more research is conducted on the technique and outcomes of implanting the HM3 device in younger children, it is expected that the HM3 device will further replace the HVAD [12–14].

Table 4: Adverse events in congenital heart disease versus non-congenital heart disease patients

	All ($n = 590$)*			CHD ($n = 98$)			Non-CHD ($n = 479$)			P**
	Number of events	Number of patients (%)	Events per patient-year	Number of events	Number of patients	Events per patient-year	Number of events	Number of patients	Events per patient-year	
Pump thrombosis	377	132 (22.4)	0.925 (0.834–1.024)	105	26 (26.5)	2.253 (1.843–2.727)	272	106 (22.1)	0.788 (0.697–0.888)	<0.001
Device malfunction other than pump thrombosis	72	50 (8.5)	0.177 (0.138–0.223)	18	11 (11.2)	0.386 (0.229–0.610)	54	39 (8.1)	0.156 (0.118–0.204)	<0.001
Infection	250	107 (18.1)	0.614 (0.54–0.695)	42	18	0.901 (0.649–1.218)	208	90	0.603 (0.524–0.691)	0.017
Sepsis	57									
Pump-related	91									
Mediastinal	5									
Peripheral	7									
Wound	11									
Pulmonary	26									
Gastro-intestinal	2									
Urinary tract	5									
Other	14									
Unspecified	32									
CVA	154	126 (21.4)	0.378 (0.321–0.443)	19	17 (17.3)	0.408 (0.245–0.637)	135	109 (22.8)	0.391 (0.328–0.463)	0.867
Ischaemic	53									
Haemorrhagic	45									
Unspecified	56									
Bleeding	111	80 (13.6)	0.273 (0.224–0.328)	17	13 (13.3)	0.365 (0.213–0.584)	94	67 (14.0)	0.272 (0.220–0.333)	0.267
Intrathoracic	49									
Pump-related	17									
Abdominal	13									
Retroperitoneal	8									
Other	8									
Unspecified	16									
Cardiac arrhythmia	75	35 (5.9)	0.184 (0.145–0.231)	0	0	–	75	35 (7.3)	0.217 (0.171–0.273)	0.002
Right ventricular failure	50	50 (8.5)	0.123 (0.091–0.162)	4	4 (4.1)	0.086 (0.023–0.220)	36	36 (7.5)	0.104 (0.073–0.144)	0.711
With secondary RVAD placement	35	35								
Respiratory failure	30	25 (4.2)	0.074 (0.050–0.105)	7	7 (7.1)	0.150 (0.060–0.309)	23	18 (3.8)	0.067 (0.0423–0.100)	0.053
Pericardial fluid collection	25	19 (3.2)	0.061 (0.040–0.091)	1	1 (1.0)	0.021 (0.001–0.120)	24	18 (3.8)	0.070 (0.045–0.103)	0.223
Requiring surgical intervention	18									
Renal dysfunction	16	16 (2.7)	0.039 (0.022–0.064)	2	2 (2.0)	0.043 (0.005–0.155)	14	14 (2.9)	0.041 (0.022–0.068)	0.941
Arterial non-CNS thromboembolism	11	11 (1.9)	0.027 (0.013–0.048)	4	4 (4.1)	0.086 (0.023–0.220)	7	7 (1.5)	0.020 (0.014–0.117)	0.012

Adverse events are reported according to the INTERMACS definitions [6].

*7 unknown primary diagnosis; 6 valvular heart disease.

**Difference in adverse event rates between groups with and without congenital heart disease.

CHD: congenital heart disease; CNS: central nerve system; CVA: cerebrovascular accident; RVAD: right ventricular assist device.

Table 5: Adverse events in patients supported by a pulsatile flow device versus a continuous flow device

	Pulsatile flow-supported ($n = 367$)				Continuous flow-supported ($n = 215$)				P**
	Number of events	Number events <30d	Number of patients (%)	Events per patient-year	Number of events	Number of events < 30d	Number of patients	Events per patient-year	
Pump thrombosis	309	91	105 (28.6)	1.822 (1.624–2.037)	68	13	27 (12.6)	0.289 (0.224–0.366)	<0.001
Device malfunction other than pump thrombosis	62	16	42 (11.4)	0.366 (0.280–0.469)	10	2	8 (3.7)	0.042 (0.020–0.078)	<0.001
Infection	96	33	79 (21.5)	0.566 (0.458–0.691)	153	26	52 (24.2)	0.650 (0.551–0.761)	0.288
CVA	103	43	87 (23.7)	0.607 (0.496–0.737)	50	21	38 (17.7)	0.212 (0.158–0.28)	<0.001
Bleeding	59	42	45 (12.3)	0.348 (0.265–0.449)	52	35	35 (16.3)	0.221 (0.165–0.290)	0.016
Cardiac arrhythmia	11	6	10 (2.7)	0.065 (0.032–0.116)	64	24	25 (11.6)	0.272 (0.209–0.347)	<0.001

*8 patients with unknown mode of support.

**Difference in adverse event rates between pulsatile flow-supported and continuous flow-supported patients.

CVA: cerebrovascular accident.

Aetiology

When examining the patient populations, it is evident that the most prevalent cause of heart failure in paediatric patients receiving VAD therapy is DCM. Only 17% of the patients have an underlying CHD, which represents a slight increase compared to the previously reported 15% in the third Paedi-EUROMACS report [2]. However, it is important to note that the proportion of patients with CHD remains significantly lower than the reported 25% in the recent North American report [9].

Mortality

The overall actual mortality probability at 2 years on VAD support, similarly to the previous report, was 22.0% but differed depending on the underlying cause of heart disease. Non-CHD patients had a lower probability of mortality at 2 years of follow-up (20.4%), whereas those with a CHD had a probability of mortality of 30.8% ($P = 0.009$). Significant differences in patient characteristics between these 2 groups could explain much of the variation in survival. Patients with CHD were younger, had a lower BSA and lower weight (2.5 years vs 8 years $P < 0.001$, 0.6 m^2 vs 0.9 m^2 $P = 0.012$, 11.6 kg vs 20.0 kg $P < 0.001$, respectively). Previous studies have confirmed that younger patients tend to have lower overall survival rates [15, 16]. This divergence in survival rates among younger patients may be attributed, in part, to the increased utilization of paracorporeal pulsatile flow devices in these individuals, which has been linked to higher rates of adverse events such as thrombosis and embolic events [17, 18]. However, multivariable analyses did not show a significant association between either aetiology (CHD/non-CHD), BSA or type of support (pulsatile/continuous flow) and mortality (HR 1.285, $P = 0.285$, HR 0.994, $P = 0.858$, HR 1.379, $P = 0.124$).

The difference in probability of mortality between the CHD and the non-CHD group might be explained, however, by the difference in INTERMACS profile and previous ECMO support. Patients with CHD had a significantly worse INTERMACS profile when implanted and were more often previously supported by ECMO compared to non-CHD patients. Moreover, a worse INTERMACS profile and prior ECMO support were significantly correlated with higher mortality rates in multivariable analyses (HR 0.582, $P = 0.042$; HR 1.804, $P = 0.003$), indicating a generally poorer clinical condition. This finding could imply that a substantial portion of these CHD patients underwent emergency VAD implants due to post-cardiotomy heart failure. Indeed, 53% of patients with CHD had undergone previous cardiac operations compared to only 6.9% of non-CHD patients. However, how much time passed between the last operation and the moment the VAD was implanted is not recorded in the EUROMACS database.

Finally, lower donor availability in smaller children and regional differences in donor availability are likely to influence waiting list time and therefore mortality during VAD support [19].

Transplant and weaning

In the current report, the probability of explantation has shown a slight increase, rising from 7.5% to 9.3% at 1 year of VAD support [2]. When comparing the 1-year transplant-free and explant-free survival rates between this report and the North American report, a noticeable difference can be observed, especially between the CHD subgroups [9]. In this cohort, the actual probability of being alive on a device after 1 year of support was 20.5%, whereas the North American cohort demonstrated an actuarial probability of 9% remaining on a device after the same duration. Within our CHD subgroup, 20.1% had a probability of being alive after 1 year of VAD support, as opposed to only 7.2% in the United States. Besides the different methods, this difference can be partly explained by the fact that the Pedimacs registry includes short-term devices in contrast to the Paedi-EUROMACS report. Furthermore, this difference can be attributed to the higher probability of a transplant in the United States. Although this current report shows an increase in the transplant probability after 1 year from 45.1% to 49.9%, it still falls short of the reported rate of 65.6% in the Pedimacs report.

Adverse events

The occurrence of pump thrombosis remains the primary adverse event during the support period. Infection and stroke are the second and third most frequent events, with rates of 0.614 and 0.378 events per patient year (18.1% and 21.4% of the patients), respectively. The North American Pedimacs registry

reported an incidence of 29% infection and 11% CVA [9]. When considering different rates of complications between different registries, several nuances must be appreciated. The aforementioned inclusion of short-term assist devices in the Pedimacs registry results in cases being included with shorter transplant wait times. This in turn reduces the median duration of circulatory support and therefore the period at risk of adverse events.

Pump thrombosis and infection occurred significantly more often in the CHD group than in the non-CHD group. Aetiology (CHD vs non-CHD) was significantly associated with pump thrombosis and this association was interestingly still significant even after adjusting for the impact of size (BSA) and the type of support (pulsatile/continuous) (HR 1.641, $P = 0.028$). Altered anatomy due to previous corrective surgery might partly explain this relationship.

Additionally, pulsatile flow support is well-known to influence thromboembolic complications [6, 20]. This report reflects this relationship as well. When comparing patients supported with a pulsatile flow to those supported with a continuous flow device, pump thrombosis, CVA and bleeding occurred significantly more frequently in the pulsatile flow-supported group. Pulsatile flow support was even found to be significantly associated with pump thrombosis in multivariable analyses (HR 2.345, $P = 0.001$). Arrhythmias occurred significantly more often in the non-CHD group, which might be explained by the fact that in cardiomyopathy and myocarditis, the cardiac muscle tissue itself is affected, which can trigger arrhythmias.

Future directions

In the future we will continue to expand the EUROMACS database network. Ongoing efforts are made to recruit more centres. Increasing our network allows us to better support clinicians in performing evidence-based medicine.

Limitations

EUROMACS does not require mandatory participation. As a result, continuous efforts are being made to monitor and enhance the quality of data. Similar to other international multicentre registries, we face challenges with missing data and incomplete follow-up, which can introduce bias. It is important to note that the data are observational in nature, which means that unaddressed confounding factors may impact the outcomes. Furthermore, only durable devices are included in the EUROMACS database.

CONCLUSION

This fourth Paedi-EUROMACS report highlights the increasing use of paediatric VADs, with approximately 120 primary VAD implants being performed annually. The selection of VADs is influenced by various factors, such as patient age and size. The patient populations with CHD and non-CHD exhibit distinct characteristics, resulting in varying risk profiles and unsurprising differences in mortality and transplant rates.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

ACKNOWLEDGEMENTS

We are grateful to the medical doctors, ventricular assist device coordinators and data managers who submitted the data from the participating hospitals to EUROMACS.

FUNDING

The European Association for Cardio-Thoracic Surgery supported this study and made resources available to execute this work. Oliver Miera and Eugan Sandica received institutional grants (travel fees, speaker honoraria) from Berlin Heart. The employer of Kevin Damman receives speaker/consultancy fees from Abbott, Boehringer Ingelheim, AstraZeneca, FIRE1 and Echosens.

Conflict of interest: none declared.

DATA AVAILABILITY

The data underlying this article are available in the article and in its online supplementary material. All relevant data are within the manuscript and its Supporting Information files.

Author contributions

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Reviewer information

The *European Journal of Cardio-Thoracic Surgery* thanks Suvitesh Luthra and the other anonymous reviewers for their contribution to the peer review process of this article.

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European Journal of Cardio-Thoracic Surgery, 2024, 66, 1–12
https://doi.org/10.1093/ejcts/ezae276
Original article