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Outcomes of children with congenital heart disease implanted with ventricular assist devices: An analysis of the Pediatric Interagency Registry for Mechanical Circulatory Support (Pedimacs)

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BACKGROUND: The reported ventricular assist device (VAD) experience in the pediatric congenital heart disease (CHD) population is limited. We sought to describe contemporary use and outcomes of VADs in children with CHD and compare these outcomes to those of non-CHD children.

METHODS: Patients enrolled in the Pediatric Interagency Registry for Mechanical Circulatory Support (Pedimacs) between September 19, 2012 through June 30, 2017 were included. CHD was classified as biventricular vs single ventricle (Stages 1, 2, or 3). Outcomes were compared between groups and multivariable analysis was used to identify factors associated with mortality on the device.

RESULTS: Among the 471 patients enrolled, 108 (24%) had CHD (45 biventricular and 63 single ventricle). CHD patients were younger (5.7 ± 5.7 years vs 9.8 ± 6.5 years; $p < 0.0001$) and smaller (0.8 ± 0.5 m^2 vs 1.2 ± 0.7 m^2; $p < 0.0001$) compared with non-CHD patients. CHD patients were more likely to receive a paracorporeal continuous-flow VAD (36.1% vs 12.9%; $p < 0.0001$) and less likely to receive an implantable continuous-flow VAD (27.8% vs 55.0%; $p < 0.0001$) compared with non-CHD patients. After 6 months on a VAD, CHD patients had higher mortality (36.4% vs 12.1%) and a lower transplantation rate (29.1% vs 59.9%) than non-CHD patients ($p < 0.0001$). In the multivariable analysis, CHD was the factor most strongly associated with mortality on VAD (hazard ratio [HR] = 2.9; $p < 0.0001$), whereas the factors implantable continuous-flow device and high-volume center were protective (HR = 0.3, $p < 0.0001$, and HR = 0.6, respectively; $p = 0.02$).

CONCLUSIONS: VAD use in children with CHD is associated with increased mortality and decreased transplant rates compared to children without CHD. For the subgroup of children with

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CHD who received implantable continuous-flow VADs, survival rates were higher and comparable to those of children without CHD. Increased experience correlated with better survival in pediatric VADs.
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Congenital heart disease (CHD) is the most common etiology of heart failure in hospitalized children and accounts for approximately 40% of all pediatric heart transplants.[1,2] CHD is one of the strongest risk factors associated with waiting list mortality among children listed for heart transplant.[3,4] Despite the overall growth and progress made in supporting pediatric heart failure patients with ventricular assist devices (VADs), the use of VADs in CHD is limited and outcomes reported thus far have been sub-optimal.[5−8] There is no consensus as to whether, when, and how VADs should be utilized in this complex, high-risk population.[9] The specific aims of this study were to: (1) describe the contemporary use, characteristics, and outcomes of children with CHD implanted with VADs; and (2) compare VAD outcomes among children with and without CHD.

Methods

The Pediatric Interagency Registry for Mechanical Circulatory Support

The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) is a national prospective database of >20,000 patients supported on devices.[10] The Pediatric Interagency Registry for Mechanical Circulatory Support (Pedimacs), the pediatric component of INTERMACS, began enrolling children with pediatric-specific data elements on September 19, 2012. Pedimacs contains data on all devices used in pediatric patients (age <19 years at device implantation) and was collecting data from 45 centers at the time of this analysis. The registry is a collaboration between the Society of Thoracic Surgery (STS), National Heart, Lung, and Blood Institute (NHLBI), the Food and Drug Administration, the Centers for Medicare and Medicaid Services, industry, and implanting centers.

Between September 19, 2012 and June 30, 2017, patients prospectively enrolled in Pedimacs comprised the study cohort. Patients with a prior heart transplant who underwent VAD implant for graft failure were excluded. Patients were enrolled at the time of their implantation and follow-up data collected at specified intervals. Patients were censored when they met a study end-point defined as death, transplant, recovery, or cessation of support.

Definitions

Patients with CHD were identified by searching the following Pedimacs variables: “primary diagnosis”; “secondary diagnosis”; “previous cardiac operation”; “previous congenital cardiac surgery”; and “concomitant surgery.” CHD was classified as biventricular or single ventricle. Single ventricle patients were further grouped into Stage 1 (e.g., unrepaired, banded, or shunted), Stage 2 (e.g., status after superior cavopulmonary anastomosis, or “Glenn”), or Stage 3 (e.g., status after total cavopulmonary anastomosis, or “Fontan”). For this study, VAD denotes a device implanted into the systemic ventricle (or adjacent atrium), regardless of the underlying morphology. Right VAD (RVAD) denotes a device implanted into the sub-pulmonary ventricle (or right atrium). Each study patient was reviewed by pediatric cardiologists (D.M.P. and S.J.K.) to ensure that the diagnoses were accurate. If there were incongruities or missing data, the inputting center was contacted to clarify the data. Previously reported Pedimacs adverse event definitions were used.[11] With respect to center volume, “high volume” was defined as enrolling ≥15 patients and “low volume” was defined as enrolling <15 patients during the study period.

Statistical analysis

Baseline characteristics for the pediatric patients are presented as mean ± standard deviation or count (percent). Comparisons were made using the chi-square test for categorical variables or Fisher’s exact test, as appropriate, and one-way analysis of variance was used for continuous variables. Survival after device implantation among groups was compared using Kaplan–Meier survival analysis. The mutually exclusive patient outcomes of death, transplant, or alive on a device were analyzed using competing outcomes methods. Adverse event rates were calculated within 3 months (“early”) and beyond 3 months (“late”) after implant. Risk factors for death on device were examined using Cox proportional hazard. Covariables for the multivariable analysis were chosen a priori by the authors based on clinical experience and included: age; gender; race; body surface area; patient profile; device classification; device strategy; albumin; bilirubin; sodium; blood urea nitrogen; creatinine; estimated glomerular filtration rate (eGFR); white blood cell count; platelet count; CHD; single ventricle CHD; any previous extracorporeal membrane oxygenation (ECMO); ECMO during implant hospitalization; pulmonary disease; history of malnutrition; and high-volume center. Data were analyzed using SAS statistical software version 9.4 (SAS Institute, Inc., Cary, NC). All statistical tests were two-sided and $p < 0.05$ was considered statistically significant.

Results

Study population and contemporary practice

Among the 471 patients enrolled in Pedimacs during the study period, 21 with graft failure were excluded. In the remaining 450 patients, 108 had CHD and 342 did not have CHD. Of the 108 CHD patients, 45 had biventricular CHD and 63 had single ventricle CHD. There were 23 Stage 1 patients, 21 Stage 2 patients, and 19 Stage 3 patients.

Compared with non-CHD patients at the time of VAD implant, CHD patients were younger (5.7 ± 5.7 years vs 9.8 ± 6.5 years; $p < 0.0001$), more likely to be male (65.7% vs 54.7%; $p = 0.04$), smaller (0.8 ± 0.5 m^2 vs 1.2 ± 0.7 m^2; $p < 0.0001$), and more likely to have had a previous

cardiac operation (93.5% vs 25.7%; $p < 0.0001$). CHD patients had higher hemoglobin (12.8 ± 2.1 g/dl vs 11.4 ± 1.9 g/dl; $p < 0.0001$), bilirubin (2.9 ± 4.9 mg/dl vs 1.5 ± 2.0 mg/dl; $p < 0.0001$), sodium (139.7 ± 7.8 mEq/liter vs 137.0 ± 6.1 mEq/liter; $p = 0.0002$), and international normalized ratio (1.6 ± 0.9 vs 1.4 ± 0.5; $p = 0.0008$). Of note, CHD and non-CHD patients had similar renal function, previous mechanical circulatory support use, INTERMACS patient profile, and device strategy (bridge to transplant, bridge to candidacy, destination therapy, etc.). CHD patients were more likely to receive a paracorporeal continuous-flow device (36.1% vs 12.9%; $p < 0.0001$) and less likely to receive an implantable continuous-flow device (27.8% vs 55.0%; $p < 0.0001$) compared with non-CHD patients. Over the last several years, fewer paracorporeal pulsatile-flow devices and more implantable continuous-flow devices have been used in CHD patients (refer to Table S1 in the Supplementary Material available online at www.jhltonline.org/). Complete pre-implant characteristics for CHD and non-CHD patients are presented in Table 1a.

Within the CHD group, single ventricle patients were younger (3.8 ± 4.6 years vs 8.4 ± 6.2 years; $p < 0.0001$), smaller (0.6 ± 0.4 m^2 vs 1.0 ± 0.6 m^2; $p < 0.0001$), had higher hemoglobin level (13.6 ± 1.9 g/dl vs 11.6 ± 1.9 g/dl; $p < 0.0001$), and had worse renal function (74.7 ± 34.9 ml/min/1.73 m^2 vs 96.4 ± 42.5 ml/min/1.73 m^2; $p = 0.005$) compared with biventricular CHD patients at baseline. Single ventricle patients received more paracorporeal continuous-flow devices (50.8% vs 15.6%; $p = 0.003$) and fewer implantable continuous-flow devices (20.6% vs 37.8%; $p = 0.003$) than the biventricular group. Pre-implant characteristics divided by single vs biventricular CHD are listed in Table 1b. Among single ventricle patients, Stage 1 patients were most likely to have had previous ECMO (30.4% vs 14.3% vs 0%; $p = 0.03$) and be in critical cardiogenic shock (59.1% vs 28.6% vs 21.1%; $p = 0.01$) compared with Stage 2 and 3 patients. There were no statistically significant differences in device strategy across the CHD patient subgroups. Table 1c details the pre-implant characteristics of single ventricle patients divided by palliative stage. There were 35 CHD patients <1 year old, 26 of whom had single ventricles. Their baseline characteristics are summarized in Table 1d.

A total of 45 centers enrolled patients. Ten of the 45 (22%) centers were high volume and enrolled 275 patients (61%) of the study cohort. The remaining 175 patients (39%) were enrolled at low-volume centers. Between the 2 groups there were no significant differences with respect to CHD diagnosis, age, size, or patient profile (see Table S2 online). However, high-volume centers used proportionally more implantable continuous-flow and paracorporeal pulsatile-flow devices and fewer paracorporeal pulsatile-flow devices ($p = 0.002$).

Outcomes

In the competing outcomes analysis, CHD patients were more likely to have died (36.4% vs 12.1%; $p < 0.0001$) and were less likely to be transplanted (29.1% vs 59.9%; $p < 0.0001$) than non-CHD patients after 6 months on the device (Figure 1). In analyzing only bridge-to-transplant patients, the disparity in percent transplanted at 6 months was even more pronounced in favor of non-CHD patients (32.0% vs 74.0%; $p < 0.0001$).

Overall, CHD patients had higher mortality than non-CHD patients ($p < 0.0001$; Figure 2a). There was no difference in survival between single ventricle CHD and biventricular CHD patients ($p = 0.86$; Figure 2b). Among single ventricle patients, Stage 3 patients had significantly higher survival compared with Stage 1 and 2 patients ($p = 0.003$; Figure 2c). Comparing Stage 1 vs 2, 2 vs 3, and 1 vs 3, the p-values were 0.4, 0.002, and 0.002, respectively. Excluding all Stage 1 and 2 patients, the difference in survival between CHD and non-CHD patients narrowed but remained statistically significant ($p = 0.01$; see Figure S1 online).

We performed similar analyses while excluding patients with critical cardiogenic shock (see Figure S2 online), any previous ECMO (Figure S3 online), ECMO during VAD implantation hospitalization (Figure S4 online), bilirubin >2 mg/dl (Figure S5 online), implanted with a non-LVAD (biventricular VAD, total artificial heart, or other; see Figure S6 online), and low-volume center (Figure S7 online) and compared survival between CHD and non-CHD patients. After excluding each of these factors, the difference in survival between CHD and non-CHD patients remained statistically significant.

Compared with non-CHD patients, CHD patients had worse survival with paracorporeal pulsatile-flow devices ($p = 0.05$) and similar survival with implantable continuous-flow devices ($p = 0.5$) and paracorporeal continuous-flow devices ($p = 0.1$; Figure 3).

Eleven of 26 (42%) single ventricle CHD infants (<1 year old) died during the study period (Table 2). Of the 20 single ventricle infants on paracorporeal continuous-flow device support, 13 (65%) achieved a favorable outcome. Four of the 5 single ventricle infants supported with paracorporeal pulsatile-flow devices died (Table 2).

CHD patients had a greater frequency of early respiratory failure compared with non-CHD patients ($p \leq 0.001$; Table 3). In the subgroup analyses of device classifications, CHD patients also had higher rates of "other" serious adverse events on implantable continuous-flow devices ($p = 0.009$) and paracorporeal continuous-flow devices ($p = 0.001$), although the number of events was small overall (see Tables S3, S4, and S5 online). No statistically significant differences in rates of bleeding, infection, and neurologic dysfunction were detected between CHD and non-CHD patients.

In the multivariable modeling for risk of death on device for all patients, CHD, female gender, and decreased eGFR were associated with increased mortality. Implantable continuous-flow devices and high-volume center were independently associated with improved survival (Table 4).

Discussion

In this Pedimacs analysis, 24% of children supported with VADs had CHD. CHD was associated with worse

Table 1a Patients' Characteristics in CHD vs Non-CHD Patients ($n = 450$): Pedimacs, September 19, 2012 to June 30, 2017

Baseline characteristics	CHD patients ($n = 108$)	Non-CHD patients ($n = 342$)	p-value
Age (years)	5.7 ± 5.7 ($n = 108$)	9.8 ± 6.5 ($n = 342$)	<0.0001
Age (years)			<0.0001
<1	35 (32.4)	55 (16.1)	
1 to 5	31 (28.7)	65 (19.0)	
6 to 10	20 (18.5)	44 (12.9)	
11 to 19	22 (20.4)	178 (52.0)	
Female	37 (34.3)	155 (45.3)	0.04
Race			0.9
White	63 (58.3)	203 (59.4)	
African American	22 (20.4)	73 (21.3)	
Other	23 (21.3)	66 (19.3)	
Body surface area (m^2)	0.8 ± 0.5 ($n = 106$)	1.2 ± 0.7 ($n = 334$)	<0.0001
Blood urea nitrogen (mg/dl)	28.6 ± 17.8 ($n = 108$)	25.1 ± 16.4 ($n = 342$)	0.06
Sodium (mEq/liter)	139.7 ± 7.8 ($n = 108$)	137.0 ± 6.1 ($n = 342$)	0.0002
Potassium (mEq/liter)	3.8 ± 0.7 ($n = 108$)	3.8 ± 0.6 ($n = 342$)	1.0
Aspartate aminotransferase (U/liter)	214.7 ± 1,012.3 ($n = 101$)	223.8 ± 845.7 ($n = 334$)	0.9
Alanine aminotransferase (U/liter)	183.2 ± 897.2 ($n = 101$)	203.5 ± 618.4 ($n = 336$)	0.8
Brain natriuretic peptide (pg/ml)	1,998.3 ± 1,722.2 ($n = 44$)	2,121.5 ± 1,672.0 ($n = 162$)	0.7
Pro–brain natriuretic peptide (pg/ml)	12,783 ± 13,909 ($n = 19$)	12,996 ± 11,596 ($n = 95$)	0.9
Albumin (g/dl)	3.4 ± 0.8 ($n = 104$)	3.4 ± 0.7 ($n = 334$)	1.0
Pre-albumin (mg/liter)	163.8 ± 83.8 ($n = 27$)	182.8 ± 71.5 ($n = 116$)	0.2
White blood cell count ($\times 10^3/\mu l$)	12.0 ± 6.6 ($n = 107$)	11.1 ± 4.8 ($n = 341$)	0.1
Hemoglobin (g/liter)	127.8 ± 21.2 ($n = 108$)	113.5 ± 19.3 ($n = 341$)	<0.0001
Platelet count ($\times 10^3/\mu l$)	199.8 ± 115.2 ($n = 107$)	229.4 ± 113.7 ($n = 338$)	0.02
INR (IU)	1.6 ± 0.9 ($n = 96$)	1.4 ± 0.5 ($n = 312$)	0.0008
Uric acid (mg/dl)	7.4 ± 4.0 ($n = 20$)	7.8 ± 3.2 ($n = 98$)	0.6
Lymphocyte count (%)	17.1 ± 12.5 ($n = 79$)	23.7 ± 14.0 ($n = 253$)	0.0002
Creatinine (mg/dl)	0.6 ± 0.4 ($n = 108$)	0.8 ± 0.5 ($n = 341$)	0.009
eGFR (ml/min/1.73 m^2)	83.9 ± 39.6 ($n = 106$)	87.5 ± 48.0 ($n = 336$)	0.5
Bilirubin (mg/dl)	2.9 ± 4.9 ($n = 95$)	1.5 ± 2.0 ($n = 304$)	<0.0001
Previous cardiac operation	101 (93.5)	88 (25.7)	<0.0001
Previous ECMO	22 (20.4)	47 (13.7)	0.1
Previous MCSD	4 (3.7)	16 (4.7)	0.7
Patient profile			0.2
1—Critical cardiogenic shock	23 (37.1)	17 (38.6)	
2—Progressive decline	33 (53.2)	19 (43.2)	
3—Stable but inotrope-dependent	6 (9.7)	5 (11.4)	
4 to 7—Resting symptoms or less sick		3 (6.8)	
Pre-implant device strategy			0.3
Bridge to transplant—listed	37 (58.7)	21 (46.7)	
Bridge to candidacy	15 (23.8)	18 (40.0)	
Destination therapy	1 (1.6)		
Bridge to recovery	6 (9.5)	5 (11.1)	
Other	4 (6.3)	1 (2.2)	
Device classification			<0.0001
Implantable continuous	30 (27.8)	188 (55.0)	
Paracorporeal continuous	39 (36.1)	44 (12.9)	
Paracorporeal pulsatile	30 (27.8)	93 (27.2)	
Percutaneous	7 (6.5)	14 (4.1)	
TAH	2 (1.9)	3 (0.9)	
Pre-implant device type			0.0004
LVAD	95 (88.0)	290 (84.8)	
BiVAD	11 (10.2)	48 (14.0)	
RVAD		1 (0.3)	
TAH	2 (1.9)	3 (0.9)	

BiVAD, biventricular assist device; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; LVAD, left ventricular assist device; MCSD, mechanical circulatory support device; RVAD, right ventricular assist device; TAH, total artificial heart.

Table 1b Patients' Characteristics in Single Ventricle vs Biventricular CHD Patients ($n = 108$): Pedimacs, September 19, 2012 to June 30, 2017

Baseline characteristics	Single ventricle CHD ($n = 63$)	Biventricular CHD ($n = 45$)	p-value
Age (years)	3.8 ± 4.6 ($n = 63$)	8.4 ± 6.2 ($n = 45$)	<0.0001
Age (years)			0.0005
<1	26 (41.3)	9 (20.0)	
1 to 5	22 (34.9)	9 (20.0)	
6 to 10	10 (15.9)	10 (22.2)	
11 to 19	5 (7.9)	17 (37.8)	
Female	24 (38.1)	13 (28.9)	0.3
Race			0.3
White	33 (52.4)	30 (66.7)	
African American	15 (23.8)	7 (15.6)	
Other	15 (23.8)	8 (17.8)	
Body surface area (m^2)	0.6 ± 0.4 ($n = 61$)	1.0 ± 0.6 ($n = 45$)	<0.0001
Blood urea nitrogen (mg/dl)	32.1 ± 19.1 ($n = 63$)	23.9 ± 14.8 ($n = 45$)	0.02
Sodium (mEq/liter)	139.1 ± 7.9 ($n = 63$)	140.5 ± 7.7 ($n = 45$)	0.4
Potassium (mEq/liter)	3.8 ± 0.7 ($n = 63$)	3.8 ± 0.7 ($n = 45$)	0.5
Aspartate aminotransferase (U/liter)	123.4 ± 275.3 ($n = 57$)	332.9 ± 1,503.1 ($n = 44$)	0.3
Alanine aminotransferase (U/liter)	87.2 ± 259.9 ($n = 57$)	307.6 ± 1,325.1 ($n = 44$)	0.2
Brain natriuretic peptide (pg/ml)	2,051.2 ± 1,668.3 ($n = 27$)	1,914.2 ± 1,853.6 ($n = 17$)	0.8
Pro–brain natriuretic peptide (pg/ml)	13,389 ± 12,327 ($n = 9$)	1,2,237 ± 15,848 ($n = 10$)	0.9
Albumin (g/dl)	3.3 ± 0.9 ($n = 61$)	3.5 ± 0.7 ($n = 43$)	0.2
Pre-albumin (mg/liter)	153.0 ± 54.9 ($n = 14$)	175.5 ± 108.0 ($n = 13$)	0.5
W2hite blood cell count ($\times 10^3/\mu l$)	11.3 ± 3.5 ($n = 62$)	13.0 ± 9.3 ($n = 45$)	0.2
Hemoglobin (g/liter	136.0 ± 18.7 ($n = 63$)	116.4 ± 19.3 ($n = 45$)	<0.0001
Platelet count ($\times 10^3/\mu l$)	218.4 ± 126.8 ($n = 62$)	174.1 ± 92.1 ($n = 45$)	0.05
INR (IU)	1.9 ± 1.1 ($n = 52$)	1.3 ± 0.3 ($n = 44$)	0.001
Uric acid (mg/dl)	7.7 ± 3.1 ($n = 11$)	7.1 ± 5.1 ($n = 9$)	0.8
Lymphocyte count (%)	18.6 ± 13.7 ($n = 42$)	15.5 ± 11.0 ($n = 37$)	0.3
Creatinine (mg/dl)	0.6 ± 0.5 ($n = 63$)	0.6 ± 0.4 ($n = 45$)	1.0
eGFR (ml/min/1.73 m^2)	74.7 ± 34.9 ($n = 61$)	96.4 ± 42.5 ($n = 45$)	0.005
Bilirubin (mg/dl)	2.9 ± 4.1 ($n = 55$)	2.9 ± 5.9 ($n = 40$)	1.0
Previous cardiac operation	61 (96.8)	40 (88.9)	0.1
Previous ECMO	10 (15.9)	12 (26.7)	0.2
Previous MCSD	2 (3.2)	2 (4.4)	0.7
Patient profile			0.2
1—Critical cardiogenic shock	23 (37.1)	17 (38.6)	
2—Progressive decline	33 (53.2)	19 (43.2)	
3—Stable but inotrope-dependent	6 (9.7)	5 (11.4)	
4 to 7—Resting symptoms or less sick		3 (6.8)	
Pre-implant device strategy			0.3
Bridge to transplant—listed	37 (58.7)	21 (46.7)	
Bridge to candidacy	15 (23.8)	18 (40.0)	
Destination therapy	1 (1.6)		
Bridge to recovery	6 (9.5)	5 (11.1)	
Other	4 (6.3)	1 (2.2)	
Device classification			0.003
Implantable continuous	13 (20.6)	17 (37.8)	
Paracorporeal continuous	32 (50.8)	7 (15.6)	
Paracorporeal pulsatile	15 (23.8)	15 (33.3)	
Percutaneous	3 (4.8)	4 (8.9)	
TAH		2 (4.4)	
Pre-implant device type			0.0004
LVAD	62 (98.4)	33 (73.3)	
BiVAD	1 (1.6)	10 (22.2)	
TAH		2 (4.4)	

BiVAD, biventricular assist device; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; INR, international normalized ratio; LVAD, left ventricular assist device; MCSD, mechanical circulatory support device; RVAD, right ventricular assist device; TAH, total artificial heart.

Table 1c Patients' Characteristics in Single Ventricle Patients Divided by Stage of Palliation ($n = 63$): Pedimacs, September 19, 2012 to June 30, 2017

Baseline characteristics	Stage 1 ($n = 23$)	Stage 2 ($n = 21$)	Stage 3 ($n = 19$)	p-value
Age (years)	1.1 ± 2.4 ($n = 23$)	2.6 ± 3.1 (n = 21)	8.3 ± 4.7 (n = 19)	<0.0001
Age (years)				<0.0001
<1	17 (73.9)	9 (42.9)		
1 to 5	5 (21.7)	9 (42.9)	8 (42.1)	
6 to 10	1 (4.3)	2 (9.5)	7 (36.8)	
11 to 19		1 (4.8)	4 (21.1)	
Female	8 (34.8)	10 (47.6)	6 (31.6)	0.5
Race				0.3
White	15 (65.2)	9 (42.9)	9 (47.4)	
African American	3 (13.0)	5 (23.8)	7 (36.8)	
Other	5 (21.7)	6 (23.8)	3 (15.8)	
Body surface area (m^2)	0.3 ± 0.2 ($n = 23$)	7 (23.8)	1.0 ± 0.4 ($n = 18$)	<0.0001
Blood urea nitrogen (mg/dl)	34.4 ± 19.0 ($n = 23$)	8 (23.8)	28.8 ± 21.8 ($n = 19$)	0.6
Sodium (mEq/liter)	141.3 ± 5.9 ($n = 23$)	9 (23.8)	134.8 ± 8.6 ($n = 19$)	0.02
Potassium (mEq/liter)	3.7 ± 0.6 ($n = 23$)	10 (23.8)	3.8 ± 0.6 ($n = 19$)	0.8
Aspartate aminotransferase (U/liter)	91.0 ± 114.1 ($n = 21$)	11 (23.8)	195.0 ± 464.5 ($n = 18$)	0.4
Alanine aminotransferase (U/liter)	43.3 ± 41.2 ($n = 21$)	12 (23.8)	173.8 ± 452.9 ($n = 18$)	0.2
Brain natriuretic peptide (pg/ml)	910.8 ± 713.1 ($n = 4$)	13 (23.8)	2,134.2 ± 1,631.6 ($n = 13$)	0.3
Pro–brain natriuretic peptide (pg/ml)	20,320 ± 12,284 ($n = 5$)	14 (23.8)	614.0 ± 643.5 ($n = 2$)	0.1
Albumin (g/dl)	3.1 ± 1.3 ($n = 22$)	15 (23.8)	3.5 ± 0.4 ($n = 18$)	0.5
Pre-albumin (mg/liter)	152.0 ± 53.0 ($n = 4$)	16 (23.8)	125.2 ± 48.0 ($n = 5$)	0.3
White blood cell count ($\times 10^3/\mu l$)	10.9 ± 4.0 ($n = 22$)	17 (23.8)	10.1 ± 3.0 ($n = 19$)	0.03
Hemoglobin (g/liter)	133.0 ± 17.3 ($n = 23$)	18 (23.8)	140.0 ± 18.1 ($n = 19$)	0.5
Platelet count ($\times 10^3/\mu l$)	155.7 ± 103.6 ($n = 22$)	19 (23.8)	258.6 ± 102.8 ($n = 19$)	0.01
INR (IU)	1.6 ± 0.7 ($n = 18$)	20 (23.8)	2.6 ± 1.4 ($n = 16$)	0.008
Uric acid (mg/dl)	7.7 ± 4.2 ($n = 5$)	21 (23.8)	7.3 ± 1.7 ($n = 3$)	1.0
Lymphocyte count (%)	13.6 ± 9.2 ($n = 11$)	22 (23.8)	17.7 ± 10.0 ($n = 16$)	0.2
Creatinine (mg/dl)	0.5 ± 0.3 ($n = 23$)	23 (23.8)	0.8 ± 0.4 ($n = 19$)	0.06
eGFR (ml/min/1.73 m^2)	63.5 ± 30.2 ($n = 23$)	24 (23.8)	76.6 ± 29.7 ($n = 18$)	0.1
Bilirubin (mg/dl)	4.6 ± 6.0 ($n = 22$)	25 (23.8)	2.1 ± 1.0 ($n = 15$)	0.03
Previous cardiac operation	21 (91.3)	26 (23.8)	19 (100)	0.2
Previous ECMO	7 (30.4)	27 (23.8)	0 (0.0)	0.03
Previous MCSD	1 (4.3)	28 (23.8)	1 (5.3)	0.6
Patient profile				0.01
1—Critical cardiogenic shock	13 (59.1)	6 (28.6)	4 (21.1)	
2—Progressive decline	5 (22.7)	14 (66.7)	14 (73.7)	
3—Stable but inotrope-dependent	4 (18.2)	1 (4.8)	1 (5.3)	
Pre-implant device strategy				0.2
Bridge to transplant—listed	13 (56.5)	11 (52.4)	13 (68.4)	
Bridge to candidacy	7 (30.4)	5 (23.8)	3 (15.8)	
Destination therapy		1 (4.8)		
Bridge to recovery	3 (13.0)	3 (14.3)		
Other		1 (4.8)	3 (15.8)	
Device classification				0.0006
Implantable continuous	1 (4.3)	2 (9.5)	10 (52.6)	
Paracorporeal continuous	18 (78.3)	10 (47.6)	4 (21.1)	
Paracorporeal pulsatile	4 (17.4)	7 (33.3)	4 (21.1)	
Percutaneous		2 (9.5)	1 (5.3)	
TAH		2 (4.4)		
Pre-implant device type				0.4
LVAD	22 (95.7)	21 (100)	19 (100)	
BiVAD	1 (4.3)			

BiVAD, biventricular assist device; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; LVAD, left ventricular assist device; MCSD, mechanical circulatory support device; RVAD, right ventricular assist device; TAH, total artificial heart.

outcomes overall. In addition, CHD was found to be an independent risk factor for mortality after VAD implant and CHD patients were less likely to receive a transplant compared with non-CHD patients. Implantable continuous-flow device and high-volume center were factors independently associated with better survival. Compared with non-

Table 1d Patients' Characteristics in CHD Patients <1 Year of Age ($n = 35$): Pedimacs, September 19, 2012 to June 30, 2017

Baseline characteristics	CHD patients <1 year ($n = 35$)
Age (years)	0.4 ± 0.3 ($n = 35$)
Female	11 (31.4)
Race	
White	21 (60.0)
African American	6 (17.1)
Other	8 (22.9)
Body surface area (m^2)	0.3 ± 0.1 ($n = 35$)
Blood urea nitrogen (mg/dl)	27.6 ± 18.7 ($n = 35$)
Sodium (mEq/liter)	142.3 ± 6.6 ($n = 35$)
Potassium (mEq/liter)	3.8 ± 0.9 ($n = 35$)
Aspartate aminotransferase (U/liter)	87.6 ± 114.3 ($n = 32$)
Alanine aminotransferase (U/liter)	49.8 ± 56.7 ($n = 32$)
Brain natriuretic peptide (pg/ml)	1,907.6 ± 1,884.2 ($n = 9$)
Pro–brain natriuretic peptide (pg/ml)	14,841 ± 6,138.4 ($n = 2$)
Albumin (g/dl)	3.2 ± 1.1 ($n = 34$)
Pre-albumin (mg/liter)	176.0 ± 73.2 ($n = 3$)
White blood cell count ($\times 10^3/\mu l$)	11.4 ± 4.3 ($n = 34$)
Hemoglobin (g/liter)	12.9 ± 2.0 ($n = 35$)
Platelet count ($\times 10^3/\mu l$)	190.6 ± 127.3 ($n = 34$)
INR (IU)	1.4 ± 0.4 ($n = 28$)
Uric acid (mg/dl)	4.6 ± 1.9 ($n = 4$)
Lymphocyte count (%)	18.9 ± 11.1 ($n = 20$)
Creatinine (mg/dl)	0.5 ± 0.5 ($n = 35$)
eGFR (ml/min/1.73 m^2)	74.3 ± 38.2 ($n = 35$)
Bilirubin (mg/dl)	2.6 ± 3.3 ($n = 33$)
Previous cardiac operation	30 (85.7)
Previous ECMO	12 (34.3)
Previous MCSD	—
Patient profile	
1—Critical cardiogenic shock	15 (42.9)
2—Progressive decline	15 (42.9)
3—Stable but inotrope-dependent	5 (14.3)
4 to 7—Resting symptoms or less sick	—
Pre-implant device strategy	
Bridge to transplant—listed	17 (48.6)
Bridge to candidacy	12 (34.3)
Destination therapy	1 (2.9)
Bridge to recovery	4 (11.4)
Other	1 (2.9)
Device classification	
Implantable continuous	—
Paracorporeal continuous	21 (60.0)
Paracorporeal pulsatile	13 (37.1)
Percutaneous	1 (2.9)
TAH	—
Pre-implant device type	
LVAD	32 (91.4)
BiVAD	3 (8.6)
RVAD	—
TAH	—

BiVAD, biventricular assist device; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; INR, international normalized ratio; LVAD, left ventricular assist device; MCSD, mechanical circulatory support device; RVAD, right ventricular assist device; TAH, total artificial heart.

CHD patients, CHD patients who received implantable continuous-flow devices had similarly high survival.

To date, this report is the largest analysis of VAD use in children with CHD. Approximately 1 in 4 children who received VADs had CHD in this study. This is an increase from previous pediatric reports where the proportion of VADs implanted for CHD ranged from 16% to 17.5%.[5,12] We found that paracorporeal continuous-flow devices were commonly used in CHD, especially in smaller, single ventricle patients. Unadjusted mortality was highest for this device class but this is likely confounded by the young age, small size, acuity, and complexity of these patients. In this high-risk population, recent outcomes have most likely improved with paracorporeal continuous-flow devices as compared with the very poor survival previously reported with paracorporeal pulsatile-flow support.[7,13,14] Still, mortality has remained high and more studies and experience will be needed to determine optimal support strategies for the smaller single ventricle population.

Stage 2 patients present a unique challenge for VAD support for many reasons, including their dichotomous systemic venous return, collateral burden, and hypoxemia. Given the superior outcomes in Stage 3 patients, Stage 2 patients with severe systolic dysfunction should be considered for concomitant Fontan operation and VAD implantation (i.e., "mechanically assisted Fontan completion"), which has been reported previously.[15] Further study is warranted to determine whether this approach can improve VAD outcomes for Stage 2 patients.

Fewer CHD patients received implantable continuous-flow devices, presumably due to their smaller size and complex anatomy. However, the CHD patients who did receive implantable continuous-flow devices had similarly high survival when compared with non-CHD patients, which is consistent with the favorable implantable continuous-flow VAD outcomes in the adult CHD population.[16] In the multivariable model of the overall cohort, implantable continuous-flow devices were significantly associated with improved survival. This finding likely reflects improving VAD technology, but is also confounded by the characteristics of the patients who did, and did not, receive implantable continuous-flow devices.

CHD was found to be an independent risk factor for mortality, along with lower eGFR and female gender. The gender disparity in outcomes has also been observed in large adult studies and warrants further investigation in the pediatric population.[10,17] CHD and worse renal function have been previously linked with higher mortality in pediatric VAD studies.[7,8,18] Our analysis does not explain exactly why CHD patients are at higher risk for mortality despite attempts to control for known risk factors. The reasons for worse survival are certainly multifactorial. There was no difference in overall survival between biventricular and single ventricle, which demonstrates that the increased risk was not unique to the single ventricle patients. Anatomic complexity, chronic circulatory abnormalities, previous surgery, and related end-

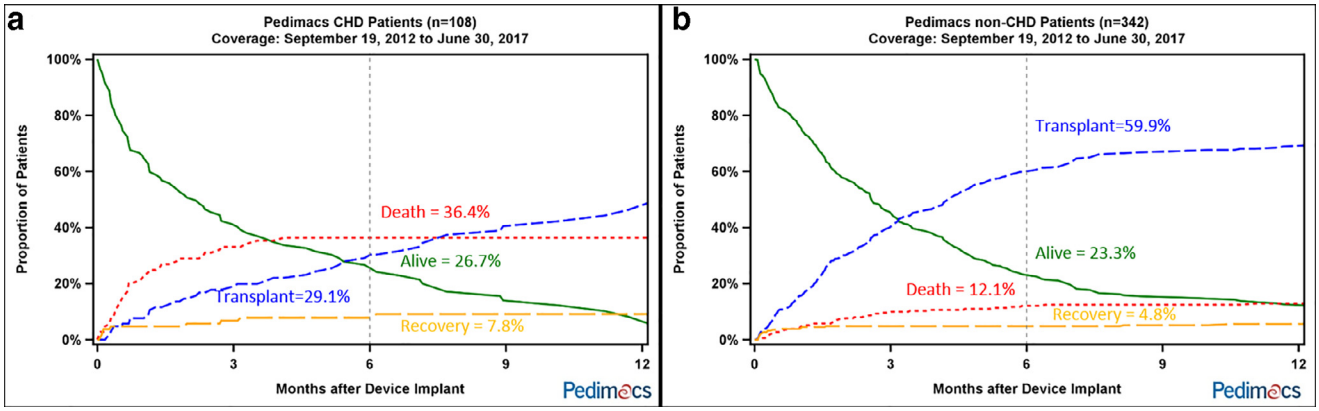

Figure 1 Competing outcomes analysis, including alive with device in place, death before transplant, transplant, and explant to recovery after VAD implant for: (a) CHD and (b) non-CHD patients.

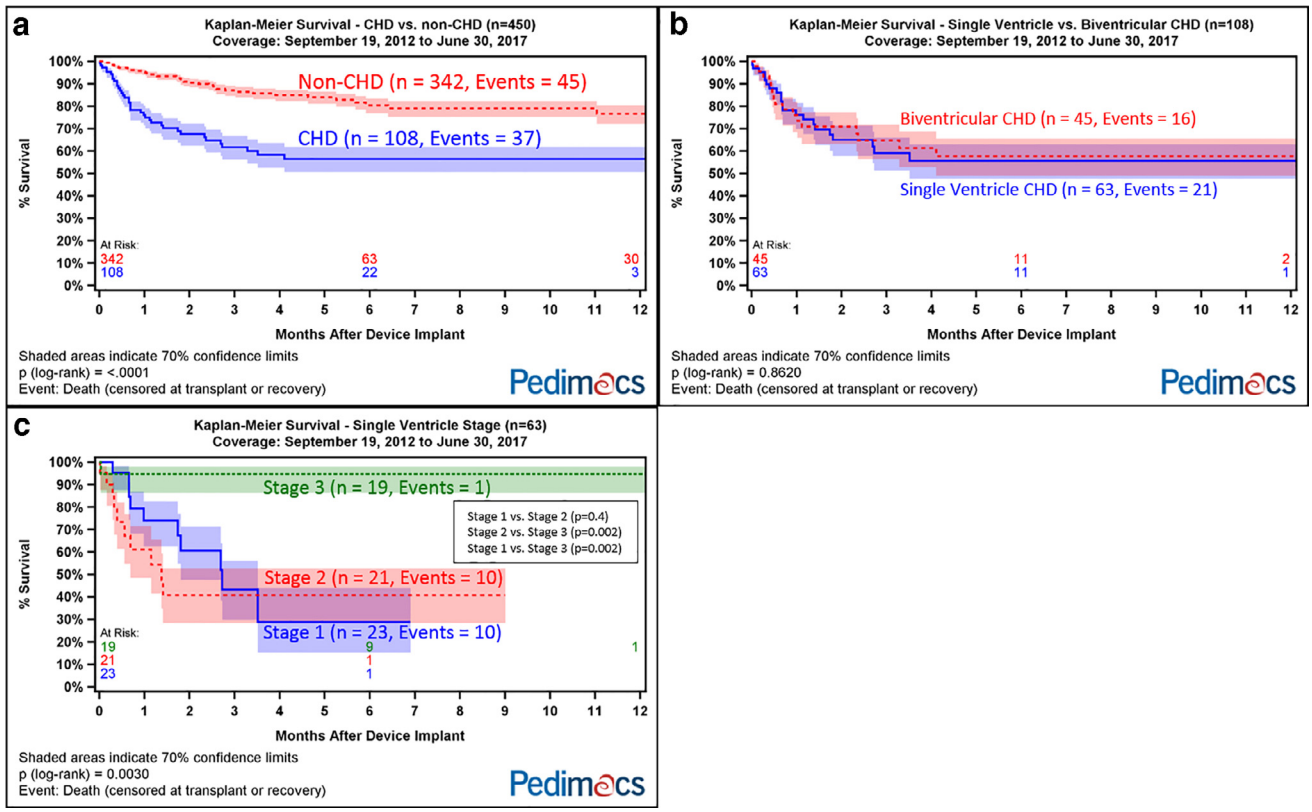

Figure 2 Kaplan–Meier survival after VAD implant divided by: (a) CHD vs non-CHD patients; (b) single ventricle CHD vs biventricular CHD; and (c) single ventricle stage.

organ effects may all contribute to the worse VAD outcomes seen in CHD.

Of note, we found that CHD patients were much less likely to have been transplanted at 6 months compared with non-CHD patients. The explanation for this likely includes differences in age and wait times, early post-VAD mortality, sensitization, and clinical status post-VAD implant between the 2 groups.

We were not surprised to find high-volume centers being associated with better survival. Morales and colleagues reported similar findings and also showed that high-volume centers had lower associated costs.[19] In our analysis comparing low- and high-volume centers, there were detectable differences in how devices were utilized. These findings support the idea that there is a steep learning curve in pediatric VAD therapy and that experience and expertise can improve outcomes. In response, the pediatric heart failure and VAD community has recently launched ACTION (the Advanced Cardiac Therapies Improving Outcomes Network) to foster more active sharing and collaboration between centers and to ultimately drive improvement in critical outcomes collectively.

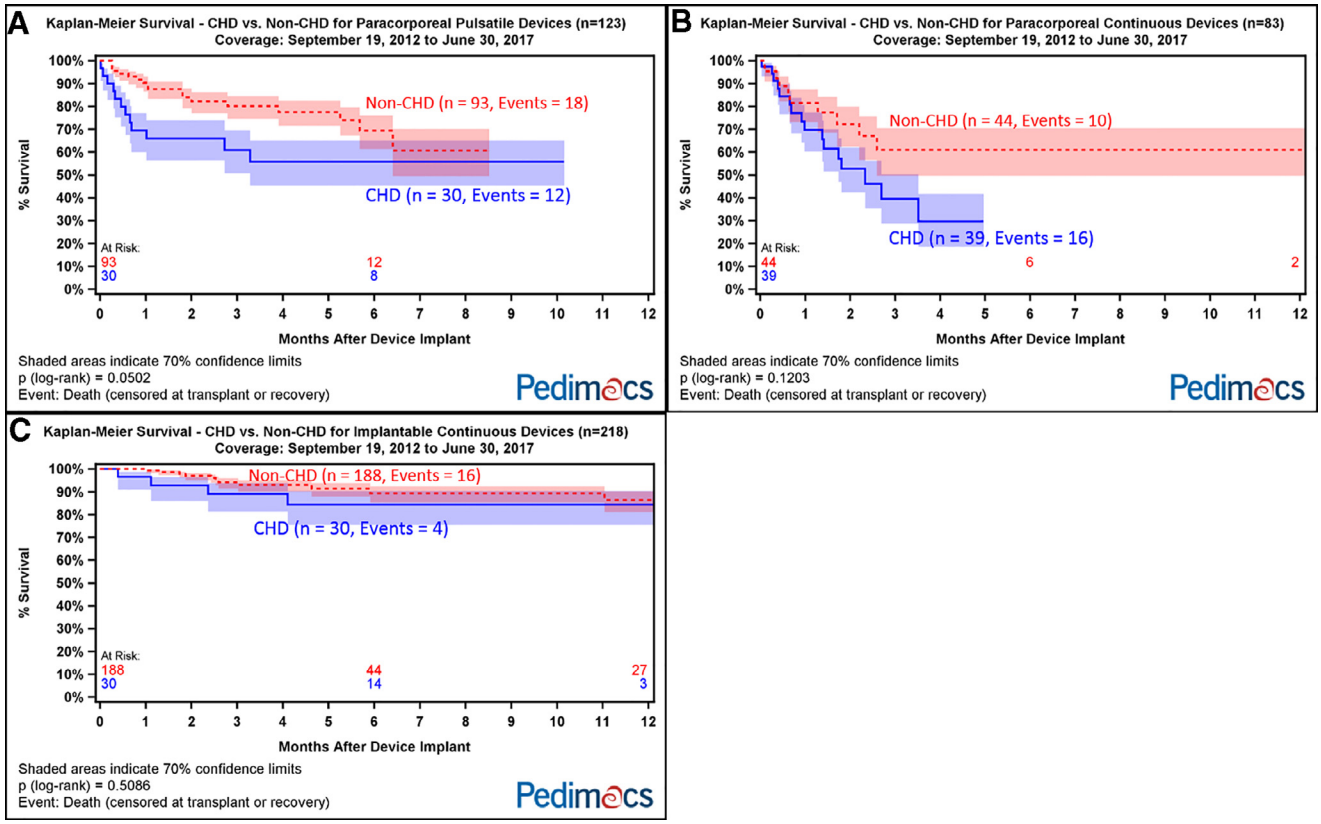

Figure 3 Kaplan–Meier survival after VAD implant for CHD vs non-CHD patients for: (a) paracorporeal pulsatile devices; (b) paracorporeal continuous devices; and (c) implantable continuous-flow devices.

Table 2 Outcomes for CHD Patients <1 Year of Age as of June 30, 2017 ($n = 35$): Pedimacs, September 2012 through June 2017

Outcome	SV (paracorporeal continuous) ($n = 20$)	SV (paracorporeal pulsatile) ($n = 5$)	SV (percutaneous) ($n = 1$)	BV (paracorporeal continuous) ($n = 1$)	BV (paracorporeal pulsatile) ($n = 8$)
Alive	4 (20%)	1 (20%)			
Transplanted	4 (20%)		1 (100%)	1 (100%)	6 (75%)
Death	7 (35%)	4 (80%)			1(12%)
Recovery	5 (25%)				1 (12%)

BV, biventricular; SV, single ventricle.

Limitations

There are important limitations to this study. Pedimacs only captures patients from participating centers and there is likely center-to-center variability in the accuracy and completeness of the reporting. Due to the relatively small number of patients, the analysis was mostly descriptive in nature and only the strongest associations were detectable in multivariable modeling. Because of the limited numbers of patients, heterogeneity, and inability to adequately decouple the effects of age, size, and device, we did not perform an analysis for risk factors for mortality within the CHD group and subgroups. In the future, such an analysis will be possible if Pedimacs enrollment continues to increase over time. Due to significant inconsistencies in the data, we were unable to accurately analyze and compare device malfunction/pump thrombosis events and rehospitalizations in this study.

In conclusion, children with CHD have higher mortality and a lower rate of transplantation compared with children without CHD after VAD implant. Still, CHD patients supported with implantable continuous-flow devices demonstrated good survival. The experience and expertise gained at larger volume centers were shown to result in improved outcomes. Further collaboration and study are warranted to better identify and support the CHD population at highest risk.

Disclosure statement

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Table 3 Adverse Events for CHD vs Non-CHD Pedimacs Patients, September 19, 2012 to June 30, 2017

		Pedimacs CHD				Pedimacs non-CHD					
Event	Period[a]	Events	Patient count	Patient percent	Rate[b]	Events	Patient count	Patient percent	Rate[b]	Rate ratio[c]	*p*-value[d]
Arterial non-CNS thromboembolism	Early					3	3	1%	0.5		
Bleeding	Early	33	24	22%	17.9	131	89	26%	19.9	0.9	0.6
	Late	5	4	4%	3.2	12	10	3%	1.4	2.3	0.1
Cardiac arrhythmia	Early	11	8	7%	6	30	24	7%	4.6	1.3	0.4
	Late					2	2	1%	0.2		
Hepatic dysfunction	Early	2	2	2%	1.1	7	7	2%	1.1	1	1.0
	Late					2	2	1%	0.2		
Infection	Early	33	23	21%	17.9	93	70	20%	14.1	1.3	0.2
	Late	9	6	6%	5.8	38	26	8%	4.5	1.3	0.5
Neurologic dysfunction	Early	33	25	23%	17.9	87	71	21%	13.2	1.4	0.1
	Late	4	4	4%	2.6	20	12	4%	2.3	1.1	0.9
Other SAE	Early	33	22	20%	17.9	113	68	20%	17.2	1	0.8
	Late	6	5	5%	3.8	19	14	4%	2.2	1.7	0.2
Pericardial drainage	Early	5	5	5%	2.7	18	16	5%	2.7	1	1.0
Psychiatric episode	Early	3	3	3%	1.6	21	20	6%	3.2	0.5	0.3
	Late	1	1	1%	0.6	2	2	1%	0.2	2.7	0.4
Renal dysfunction	Early	12	11	10%	6.5	23	23	7%	3.5	1.9	0.08
	Late	1	1	1%	0.6	2	1	0%	0.2	2.7	0.4
Respiratory failure	Early	35	23	21%	19	41	34	10%	6.2	3	<0.001
	Late	2	2	2%	1.3	3	3	1%	0.4	3.6	0.1
Venous thromboembolism	Early					6	6	2%	0.9		
Wound dehiscence	Early	1	1	1%	0.5	2	2	1%	0.3	1.8	0.6
	Late					1	1	0%	0.1		

CHD, congenital heart disease; CNS, central nervous system; SAE, serious adverse event.

[a]Early: within 3 months of device implant; late: >3 months after device implant.

[b]Rates are reported per 100 patient-months.

[c]Rate ratio compares CHD rates with non-CHD rates for the given time period.

[d]*p*-value compares CHD rates with non-CHD rates for the given time period.

Table 4 Multivariable Model for Mortality on a Device ($n = 450$) for Pedimacs Patients, September 19, 2012 to June 30, 2017

Pre-implant characteristics	Hazard ratio	95% CI	*p*-value
Implantable continuous-flow device	0.3	0.2 to 0.5	<0.0001
CHD	2.9	1.8 to 4.5	<0.0001
eGFR (20-unit increase)	0.9	0.8 to 1.0	0.01
Female	1.7	1.1 to 2.6	0.02
High-volume center	0.6	0.4 to 0.9	0.02

High-volume center is defined as enrolling ≥15 patients in Pedimacs. CHD, congenital heart disease; CI, confidence interval; eGFR, estimated glomerular filtration rate.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at www.jhltonline.org/.

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