Berlin Heart®

EXCOR® Pediatric

Prospective Trial of a Pediatric Ventricular Assist Device

Review of the IDE trial results

Fraser et al., Prospective trial of a pediatric ventricular assist device. N Engl J Med. 2012;367(6):532-41

Abstract

Prospective trial of a pediatric ventricular assist device
Fraser CD Jr, Jaquiss RD, Rosenthal DN, Humpl T, Canter CE, Blackstone EH, Naftel DC, Ichord RN, Bomgaars L, Tweddell JS, Massicotte MP, Turrentine MW, Cohen GA, Devaney EJ, Pearce FB, Carberry KE, Kroslowitz R, Almond CS
N Engl J Med. 2012;367(6):532-41

Background
Options for mechanical circulatory support as a bridge to heart transplantation or recovery in children with severe heart failure are limited.

Methods
Study design: Prospective, multicenter, single-arm study
Patients (n=48) 16 years of age or younger were divided into two cohorts according to body-surface area:
Cohort 1: n=24, BSA <0.7 m^2
Cohort 2: n=24, BSA ≥0.7 to <1.5 m^2

Survival in the two cohorts was compared with survival in two propensity-score–matched historical control groups (one for each cohort, n=48 each) undergoing extracorporeal membrane oxygenation (ECMO) as bridge to heart transplantation selected from the ELSO[1] registry. The primary endpoint for the EXCOR® Pediatric VAD was time to death[2] or weaning with an unacceptable neurologic outcome[3] while the primary endpoint for the ECMO group was time to death (no data on neurologic status is available in the ELSO database).

1 Extracorporeal Life Support Organization
2 Definition death: Death while on support or within 30 days after weaning or before hospital discharge, whichever was longer
3 Definition unacceptable neurologic outcome: Either coma or the presence of profound sensory, motor, language, or cognitive impairment as assessed with the Pediatric Stroke Outcome Measure (PSOM)

Results

For EXCOR® Pediatric patients the Kaplan-Meier survival curves were significantly better for each cohort when compared to their respective ECMO control group (log-rank, P<0.001).

Overall for patients supported with EXCOR® Pediatric VAD, 88% in cohort 1 and 92% in cohort 2 were bridged to transplant or recovery with acceptable neurological outcome.

30-day survival

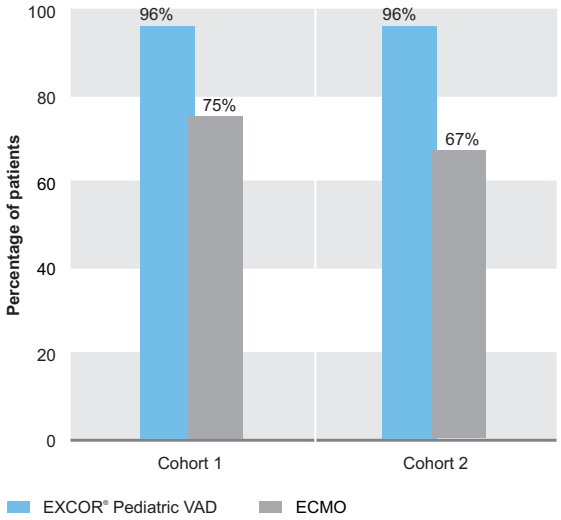


FIGURE 1 30-day survival
Survival at 30 days in cohort 1 was 96% (46% transplanted, 50% on support) for the EXCOR® Pediatric VAD group and 75% (off ECMO) for the ECMO group. In cohort 2, the 30-day survival was 96% (21% transplanted, 4% weaned, 71% on support) for the EXCOR® Pediatric VAD group and 67% (off ECMO) for the ECMO group.
The ELSO database does not specify whether patients who underwent ECMO explantation received a heart transplant or recovered.

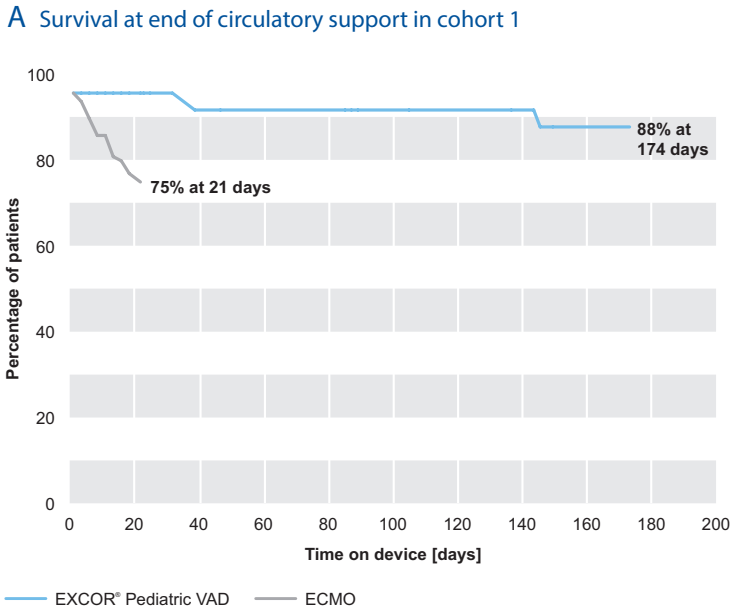
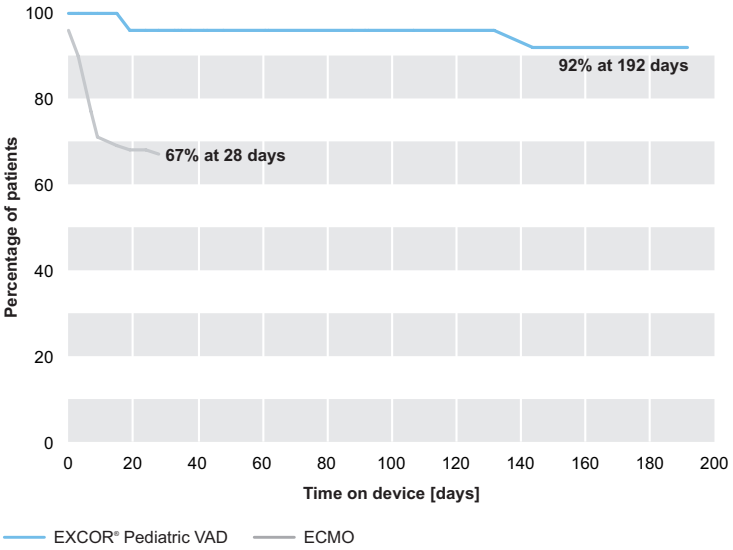


FIGURE 2 Survival at end of circulatory support in cohort 1 (A) and cohort 2 (B)
In the EXCOR® Pediatric VAD group, all patients were off the device at 174 days in cohort 1 and 192 days in cohort 2, respectively. Overall, 88% in cohort 1 and 92% in cohort 2 were bridged to transplant or recovery with acceptable neurological outcome, respectively. In the ECMO group, for cohort 1 and 2 the longest time of support was 21 days and 28 days, respectively. 25% and 33% of the patients had died on ECMO support in cohort 1 and 2, respectively.

B Survival at end of circulatory support in cohort 2



In conclusion, the ventricular assist device EXCOR® Pediatric, which is available in several sizes for use in children as bridge to transplantation or recovery, was associated with a significantly higher rate of survival, as compared with ECMO, and an acceptable rate of serious adverse events.

Data Summaries

Patient characteristics

Variable	EXCOR® Cohort 1	ECMO Cohort 1	EXCOR® Cohort 2	ECMO Cohort 2
Age in months [Median, Range]	11.7 (2.6-45.6)	10.6 (0.1-112.3)	111.2 (50.8-191.8)	138.7 (1.8-188.6)
Weight in kg [Median, Range]	9.2 (3.6-13.6)	8.8 (3.1-27.0)	30.7 (16.0-58.1)	36.0 (4.0-59.0)
BSA in m^2 [Median, Range]	0.44 (0.23-0.62)	n.a.	1.08 (0.71-1.66)	n.a.
Male/female sex (%)	50/50	n.a.	54/46	n.a.
INTERMACS profile status (%) 1 2	 46 54	 n.a. n.a.	 54 46	 n.a. n.a.
Preoperative ECMO for 10 d or less (%)	25		33	
Preoperative centrifugal VAD (%)	8		0	
Preoperative mechanical ventilation (%)	83	75	46	54
Preoperative inotrope infusion (%)	92	90	88	83
Preoperative cardiac arrest (%)	29	29	21	27
Closure of intracardiac shunt at implantation (%)	29	n.a.	12	n.a.
Valve repair or replacement at implantation (%)	8	n.a.	17	n.a.
Time (minutes) required for cardiopulmonary bypass [Average±Std]	185±49	n.a.	176±52	n.a.

Primary diagnosis EXCOR® Pediatric and ECMO patients

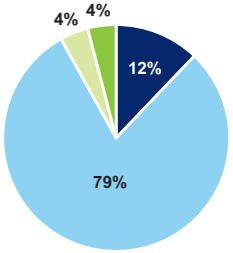


FIGURE 3 Primary diagnosis EXCOR® Pediatric – cohort 1

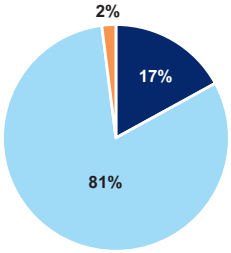


FIGURE 4 Primary diagnosis ECMO – cohort 1 control group

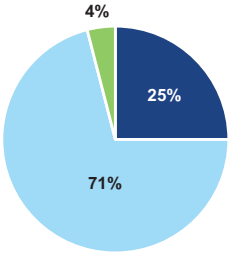


FIGURE 6 Primary diagnosis EXCOR® Pediatric – cohort 2

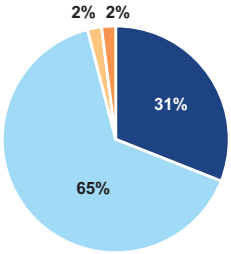


FIGURE 7 Primary diagnosis ECMO – cohort 2 control group

Type of support EXCOR® Pediatric

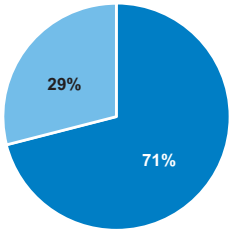
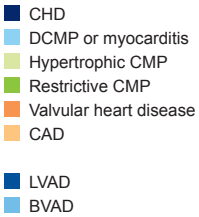


FIGURE 5 Type of EXCOR® Pediatric support – cohort 1



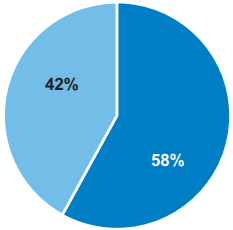


FIGURE 8 Type of EXCOR® Pediatric support – cohort 2

Competing Outcome Measures

For children in cohort 1, the median duration of support with EXCOR® Pediatric VAD was 28 days, as compared with 5 days for the matched ECMO group (P<0.001 by the Wilcoxon median two-sample test). The longest duration of support with EXCOR® Pediatric VAD and ECMO was 174 days and 21 days, respectively.

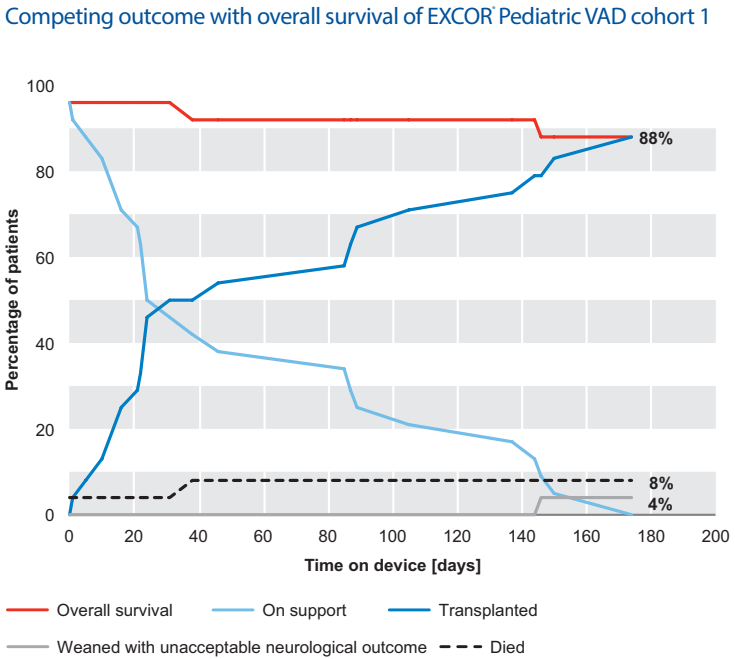


FIGURE 9 Competing outcome with overall survival of EXCOR® Pediatric VAD cohort 1
At 174 days, 88% of the patients had undergone a successful transplantation, 4% had an unacceptable neurologic outcome after weaning from the device and 8% had died. Figure adapted from Fraser et al. N Engl J Med. 2012.

The rate of survival to transplantation or recovery was markedly higher with EXCOR® Pediatric than with ECMO. The outcome comparison was particularly stringent because a successful outcome in the EXCOR® Pediatric group included an acceptable neurologic outcome, which could not be systematically analyzed in the ECMO group.

Competing outcome with overall survival of the ECMO control group for cohort 1

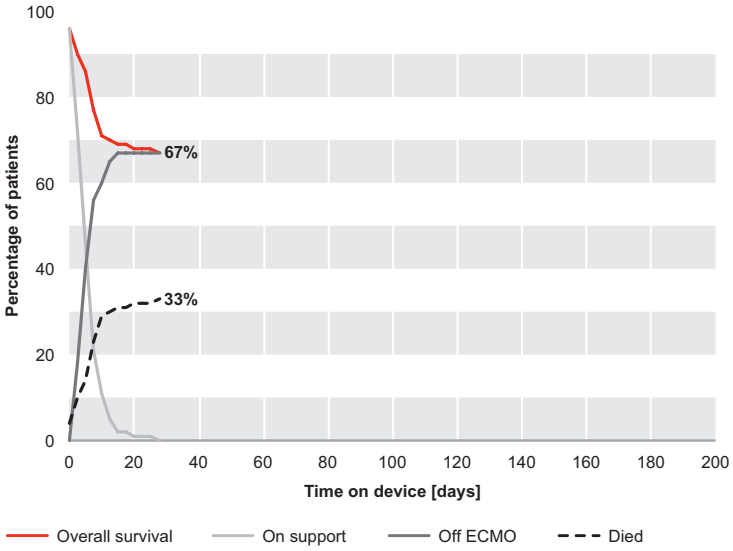


FIGURE 10 Competing outcome with overall survival of the ECMO control group for cohort 1
In the ECMO control group for cohort 1, at 21 days, 25% of the patients had died and none were alive and still on support. Figure adapted from Fraser et al. N Engl J Med. 2012.

For children in cohort 2, the median duration of support with EXCOR® Pediatric VAD was 43 days, as compared with 5 days for the matched ECMO group (P<0.001 by the Wilcoxon median two-sample test). The longest duration of support with EXCOR® Pediatric VAD and ECMO was 192 days and 28 days, respectively.

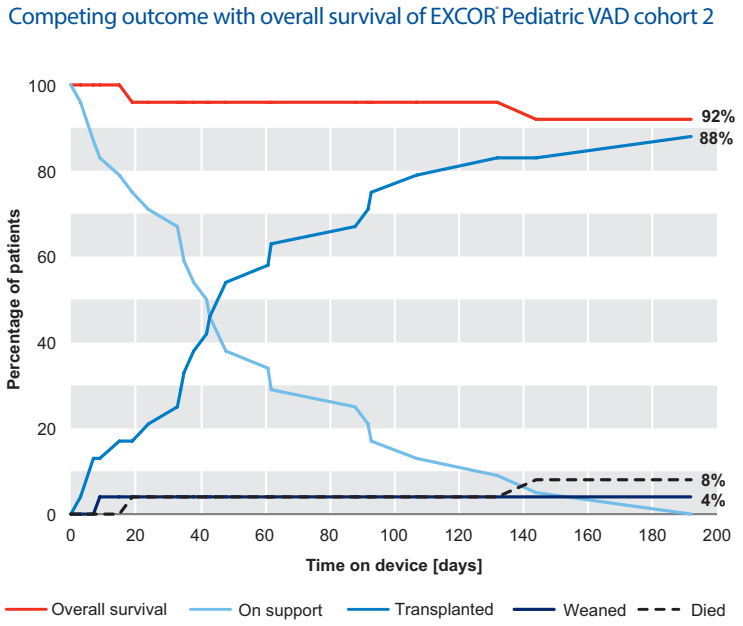


FIGURE 11 Competing outcome with overall survival of EXCOR® Pediatric VAD cohort 2
At 192 days, 92% of the patients had been transplanted or weaned. 88% of the patients had undergone a successful transplantation and 4% had been weaned successfully from the device. Figure adapted from Fraser et al. N Engl J Med. 2012.

Overall for patients supported with EXCOR® Pediatric VAD, 88% in cohort 1 and 92% in cohort 2 were bridged to transplant or recovery with acceptable neurological outcome.

Competing outcome with overall survival of the ECMO control group for cohort 2

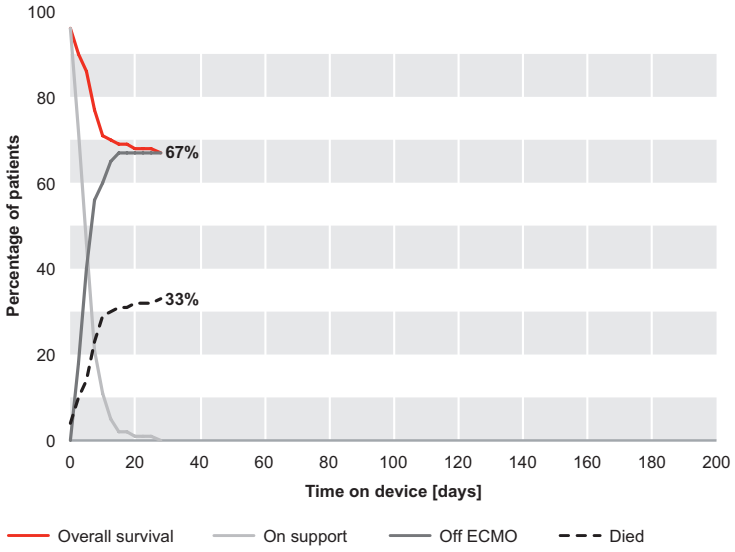


FIGURE 12 Competing outcome with overall survival of the ECMO control group for cohort 2
In the ECMO control group for cohort 2, at 28 days, 33% of the patients had died and none were alive and still on support. Figure adapted from Fraser et al. N Engl J Med. 2012.

Functional Status

Prior to implantation the majority of patients were sedated and mechanically ventilated and few were ambulatory or able to take nutrition by mouth. Within two weeks of implantation fewer patients were sedated and mechanically ventilated. Increasing proportions of participants were ambulatory and eating. Continued improvement occurred over time. For patients requiring support for three months, a further decrease in proportions requiring sedation and intubation and an increase in proportions of ambulatory patients and patients eating, was observed.

Functional status over time EXCOR® Pediatric VAD cohort 1

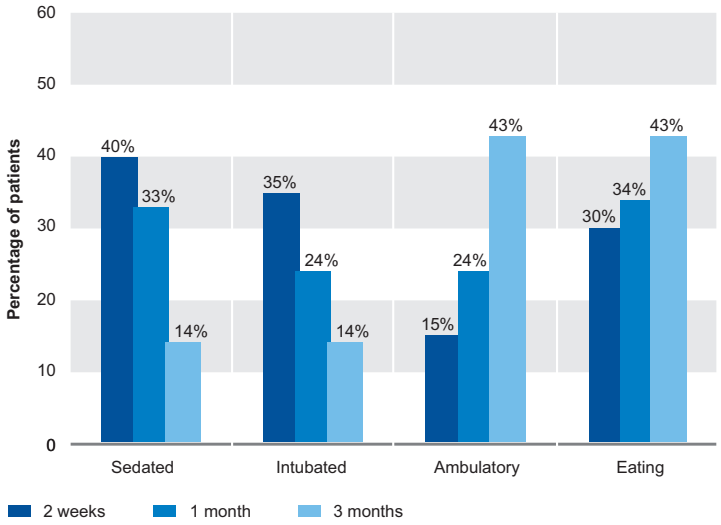


FIGURE 13 Functional status over time EXCOR® Pediatric VAD cohort 1
Prior to implantation 88% of patients were sedated and 88% mechanically ventilated. Within two weeks of implantation 40% of patients were sedated and 35% mechanically ventilated. 15% of patients were ambulatory and 30% eating). Continued improvement occurred over time. For patients requiring support for three months, a 14% required sedation and 14% intubation, 43% were ambulatory and 43% eating. Figure adapted from Fraser et al. N Engl J Med. 2012.

Functional status over time EXCOR® Pediatric VAD cohort 2

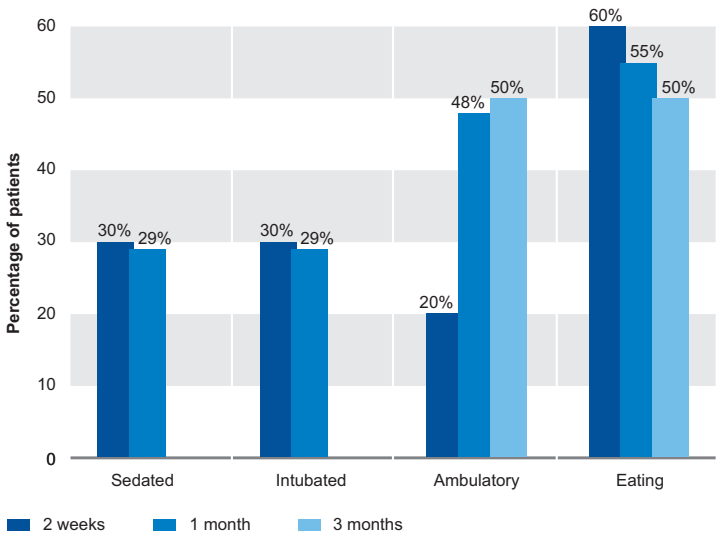


FIGURE 14 Functional status over time EXCOR® Pediatric VAD cohort 2
Prior to implantation 67% of patients were sedated and 58% mechanically ventilated. Within two weeks of implantation 30% of patients were sedated and 30% mechanically ventilated. 20% of patients were ambulatory and 60% eating. Continued improvement occurred over time. For patients requiring support for three months, no patient required sedation or intubation, 50% were ambulatory and 50% eating. Figure adapted from Fraser et al. N Engl J Med. 2012.

Freedom from Primary Endpoint

The primary endpoint for EXCOR® Pediatric VAD was defined as time to death[1] or weaning with an unacceptable neurologic outcome[2]. The primary endpoint for the ECMO control group was only defined as time to death[1], because data on neurologic status were not available in the ELSO[3] database.

Freedom from primary endpoint, cohort 1

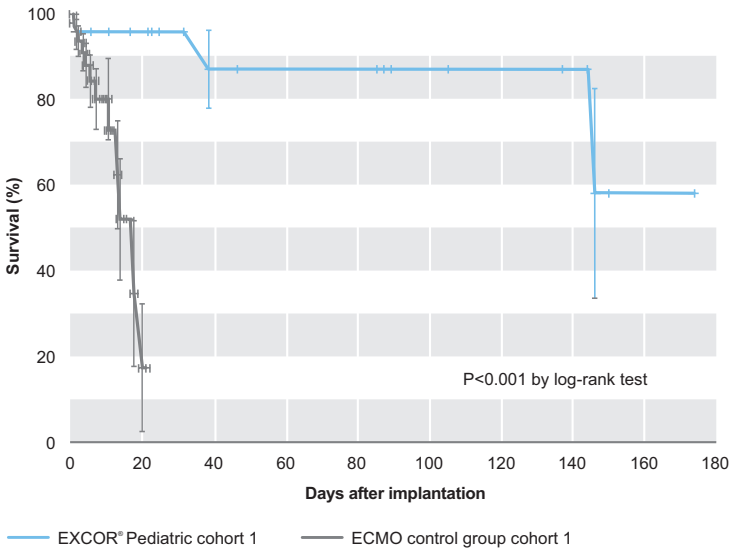


FIGURE 15 Freedom from primary endpoint, cohort 1
For EXCOR® Pediatric patients the Kaplan-Meier survival curves were significantly better for cohort 1 when compared to the respective ECMO control group (log-rank, P<0.001). Figure adapted from Fraser et al. N Engl J Med. 2012.

1 Definition death: Death while on support or within 30 days after weaning or before hospital discharge, whichever was longer
2 Definition unacceptable neurologic outcome: Either coma or the presence of profound sensory, motor, language, or cognitive impairment as assessed with the Pediatric Stroke Outcome Measure (PSOM)
3 Extracorporeal Life Support Organization

Freedom from primary endpoint, cohort 2

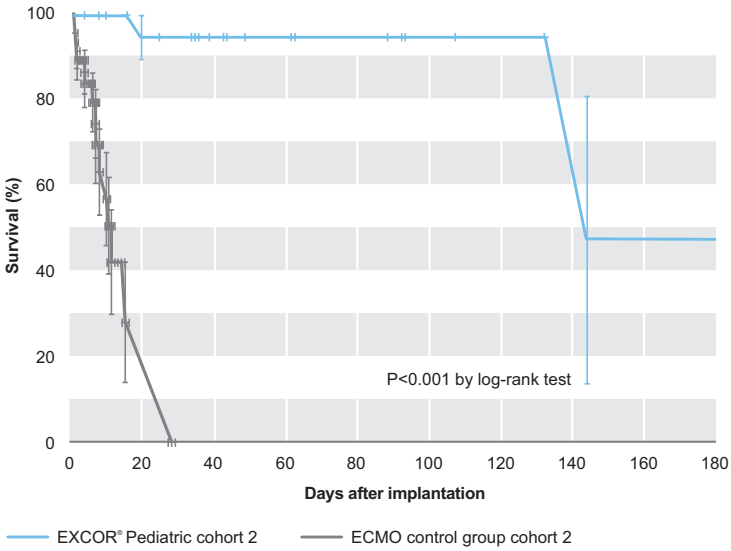


FIGURE 16 Freedom from primary endpoint, cohort 2
For EXCOR® Pediatric patients the Kaplan-Meier survival curves were significantly better for cohort 2 when compared to the respective ECMO control group (log-rank, P<0.001). Figure adapted from Fraser et al. N Engl J Med. 2012.

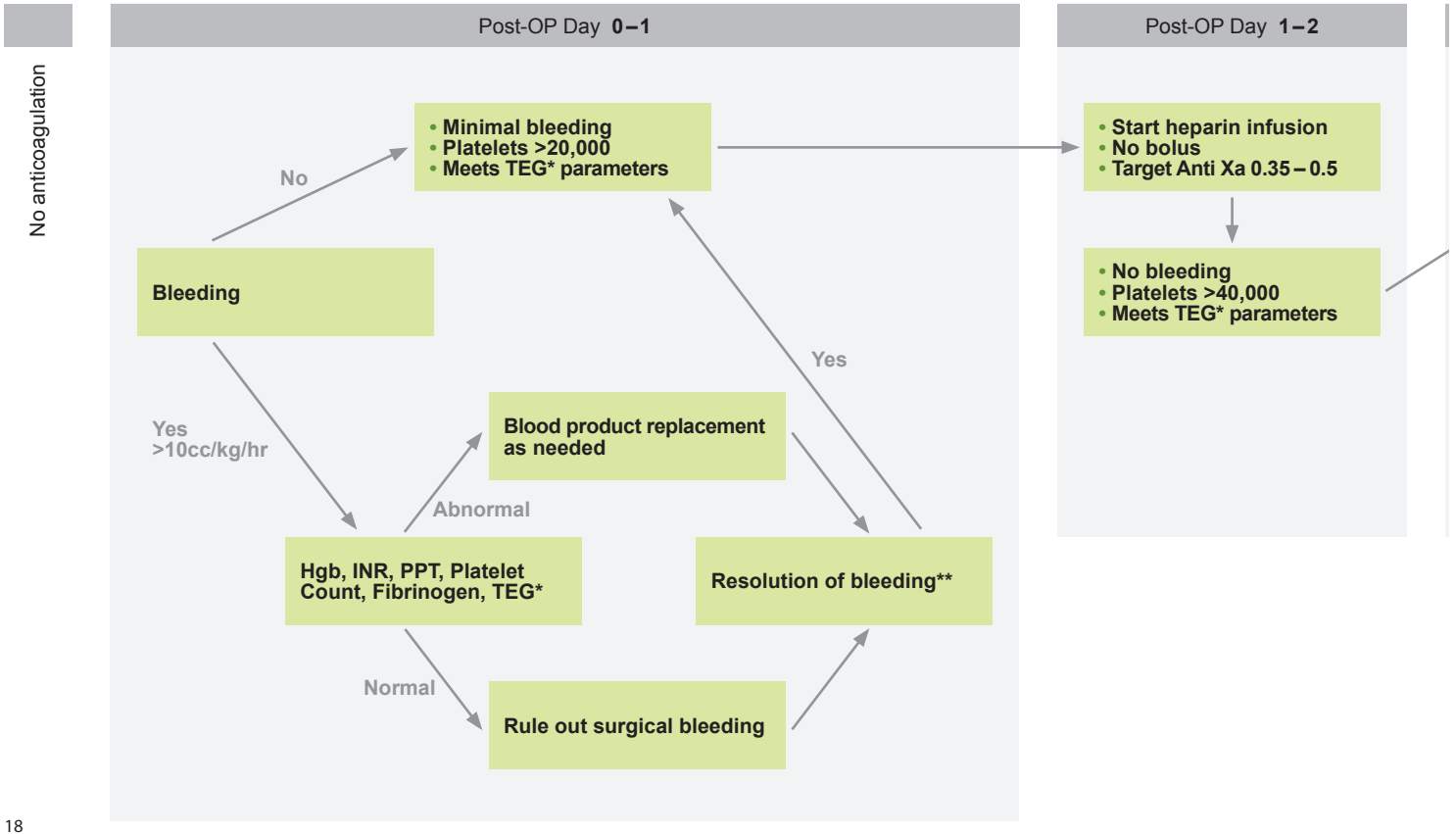
Serious Adverse Events During VAD Support

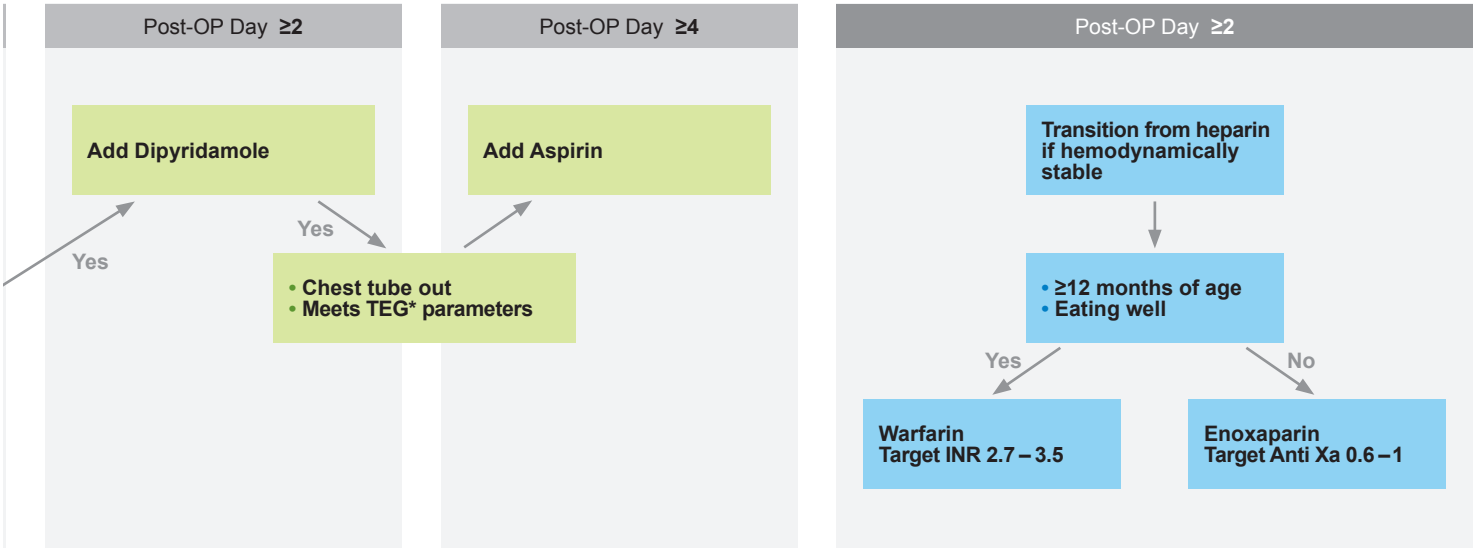
As with the use of a VAD for circulatory support in adults, serious adverse events include bleeding, infection and stroke. In total, strokes occurred in 29% of the patients (n=48). Of the patients with stroke, 50% were on ECMO or other VAD support prior to implantation of EXCOR® Pediatric VAD. The stroke rate of 29% in cohort 2 is similar to that reported in patients (BSA >1.2 m^2) who were supported with an adult-sized VAD[1]. The sequelae of stroke did not preclude eligibility for transplantation in the majority of patients. The stroke-related deficits were generally assessed as mild.
46 pump exchanges occurred in cohorts 1 & 2 combined. 43 pumps were changed due to blood clots.

1 Reinhartz et al., Multicenter experience with the Thoratec Ventricular Assist Device in children and adolescents. J. Heart Lung Transplantation, 2001

Serious Adverse Events	Patients with event cohort 1	Patients with event cohort 2
Major bleeding[1,2]	42%	50%
[1] ≥Units PRBC within 24 h during 1st 7 d post-implant (≥20 cc/kg PRBC for patients <50 kg)		
[2] Any transfusion or PRBC after 7 d post-implant		
Infection		
Localized non-device related	50%	42%
Percutaneous site	17%	0%
Internal pump component	0%	0%
Sepsis	21%	25%
Neurological dysfunction[3,4,5]	29%	29%
Ischemic	29%	29%
Hemorrhagic	0%	8%
[3] TIA		
[4] Ischemic/Hemorrhagic CVA		
[5] Patients <6 months: new abnormality head ultrasound/EEG positive for seizure activity		
Non-CNS thromboembolism		
Arterial	4%	0%
Venous	4%	0%
Hypertension	50%	33%
Device malfunction	0%	0%
Hemolysis		
Early (<72 h post-implant)	0%	0%
Late (>72 h post-implant)	4%	4%
Right heart failure	8%	13%
Cardiac arrhythmia		
Sustained ventricular (requiring defibrillation/cardioversion)	4%	8%
Sustained supraventricular (requiring drug treatment/cardioversion)	0%	13%
Pericardial fluid collection (requiring surgical intervention or percutaneous catheter drainage)		
With tamponade	4%	8%
Without tamponade	8%	8%
Respiratory failure	13%	25%
Renal dysfunction		
Acute	8%	8%
Chronic	0%	8%
Hepatic dysfunction	4%	4%
Myocardial infarction	0%	0%

Anticoagulation





* TEG = thromboelastogram
** Bleeding or clotting issues recurring during therapy are addressed in an individualized manner dependent on etiology and laboratory and clinical parameters

FIGURE 17 Recommended antithrombotic regimen
Stollery Children's Hospital, Edmonton, Alberta Canada.
Figure adapted from Fraser et al., Prospective Trial of a Pediatric Ventricular Assist Device, NEJM, 2012.

Berlin Heart®

Berlin Heart GmbH
Wiesenweg 10
12247 Berlin · Germany
Phone +49 30 81 87 - 26 00
Fax +49 30 81 87 - 26 01
info@berlinheart.de
www.berlinheart.de

Berlin Heart Inc.
200 Valleywood
Suite A-500
The Woodlands · Texas 77380
Phone +1 281 863 - 97 00
Fax +1 281 863 - 97 01
info@berlinheart.com
www.berlinheart.com

The Berlin Heart EXCOR® Pediatric Ventricular Assist Device (EXCOR® Pediatric) is approved for use by the FDA under a Humanitarian Device Exemption.

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