The Berlin Heart EXCOR® Pediatric Ventricular Assist Device for Bridge to Heart Transplantation in US Children

Running title: Almond et al.; Berlin Heart EXCOR® Pediatric VAD Outcomes

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Journal Subject Codes: Cardiovascular (CV) surgery:[37] CV surgery: transplantation, ventricular assistance, cardiomyopathy, Cardiovascular (CV) surgery:[41] Pediatric and congenital heart disease, including cardiovascular surgery, Heart failure:[110] Congestive
Abstract:

Background—Recent data suggest the Berlin Heart EXCOR Pediatric ventricular assist device (VAD) is superior to ECMO for bridge-to-heart transplant. Published data are limited to one in four children who received the device as part of the US clinical trial. We analyzed outcomes for all US children who received the EXCOR to characterize device outcomes in an unselected cohort and identify risk factors for mortality to facilitate patient selection.

Methods and Results—Multi-center prospective cohort study involving all children implanted with the Berlin Heart EXCOR® Pediatric VAD at 47 centers from 5/2007-12/2010. Multiphase non-proportional hazards modeling was used to identify risk factors for early (<2 months) and late mortality. Of 204 children supported with the EXCOR, the median duration of support was 40 days (range 1, 435). Survival at 12 months was 75% including 64% who reached transplant, 6% who recovered, and 5% who were alive on the device. Multivariable analysis identified lower weight, BIVAD support, and elevated bilirubin as risk factors for early mortality, and bilirubin extremes and renal dysfunction as risk factors for late mortality. Neurological dysfunction occurred in 29% and was the leading cause of death.

Conclusions—Use of the Berlin Heart EXCOR® has risen dramatically over the past decade emerging as a new treatment standard in the US for pediatric bridge-to-transplant. Three-quarters of children survived to transplant or recovery; an important fraction experienced neurological dysfunction. Smaller patient size, renal dysfunction, hepatic dysfunction, and BIVAD use were associated with mortality whereas ECMO pre-implant and CHD were not.

Key words: mechanical circulatory support transplantation, waitlist mortality, pediatric, ventricular assist device, heart failure, transplant, cardiac surgery
Introduction

In the United States (US), children with end-stage heart failure listed for heart transplantation (HT) face the highest wait-list mortality in transplant medicine\(^1,2\). While many factors may contribute, the lack of reliable miniaturized ventricular assist devices (VAD)—designed specifically to support infants and children with terminal heart failure who fail medical therapy—is often cited as the most important reason. Unlike adults and adolescents who have access to a wide variety of reliable FDA-approved long-term VADs, children have had none. Thus, for years, pediatric clinicians have resorted to using short-term devices like extracorporeal membrane oxygenation (ECMO) to bridge children to heart transplant despite its dismal success rate\(^3\).

In recent years, the Berlin Heart EXCOR\(^\circledR\) Pediatric VAD has emerged as an alternative to ECMO for bridging US children to transplant\(^4-6\). Recent data from the Investigational Device Exemption (IDE) trial of the EXCOR\(^\circledR\) suggest that 88-92\% of children can be bridged to transplant or recovery with a risk of neurological dysfunction of 29\%\(^7\). However, published results from this trial of 48 subjects did not capture the experience of more than 75\% of all US children implanted with the EXCOR\(^\circledR\) because they met one or more exclusion criteria, such as complex heart disease (e.g. single-ventricle lesions), significant end-organ dysfunction at implant, or surgical implantation at one of 27 centers not officially participating in the trial (see online supplement for detailed list of IDE trial selection criteria). Analysis of this larger compassionate-use cohort—in combination with the original IDE trial subjects—provides a unique opportunity (1) to describe broader trends in EXCOR\(^\circledR\)utilization in the United States, (2) to characterize the EXCOR\(^\circledR\)’s performance in an unselected cohort of children (reflecting the so-called ‘real-world’ experience with the device), and (3) to identify risk factors for mortality.
given the size and diversity of the overall cohort, to facilitate patient selection and family counseling.

Patients and Methods

Study Population and Data Source

All US children who received the Berlin Heart EXCOR® Pediatric VAD between May 9, 2007 and December 31, 2010 and included in the sponsor’s US regulatory database were identified using Berlin Heart’s regulatory database. The EXCOR is a pneumatically-driven paracorporeal blood pump manufactured in 5 sizes (10, 25, 30, 50, and 60 cc pump) and is capable of providing both left (LVAD) and biventricular (BVAD) assist device support\(^5\). The trial design, inclusion criteria and endpoints have been reported previously\(^5\). The IDE study was conducted at 17 centers in the US and Canada. Compassionate-use access to the EXCOR® was available to transplant-eligible children who did not meet clinical inclusion criteria of the trial, or who were implanted at one of the 27 non-IDE study sites. Data was gathered by study coordinators at each site using a data platform adapted from the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) database\(^8\). An independent clinical events committee adjudicated the causes of death and adverse events for patients at the 17 IDE study sites but not non-study sites. An independent data and safety monitoring board monitored the study and reviewed outcome data. The study protocol was approved by each center’s institutional review board and written informed consent was obtained for all patients.

Primary endpoint and study definitions

The primary hypothesis for this analysis was that among children supported with the EXCOR®, children with significant end-organ dysfunction at implant had higher mortality after adjusting
for patient factors than patients without significant end-organ dysfunction. The primary endpoint for this analysis was all-cause mortality during EXCOR® support. All patients were followed from the time of EXCOR® implant until transplant, death or recovery. Patients were censored at the time of transplant or recovery. Patients still alive on EXCOR® support on January 17, 2011 were censored.

End-organ dysfunction was defined as (A) renal dysfunction, estimated by the glomerular filtration rate (GFR) adjusted for age using the Schwartz Formula⁹ and categorized as moderately impaired (GFR 30-99% predicted) or severely impaired (GFR<30% predicted); and (B) hepatic dysfunction, as reflected by the total serum bilirubin level, categorized as moderately increased (0.7-1.1 mg/dL) and severely increased (≥1.2 mg/dL). All clinical and demographic variables were defined at the time of EXCOR® implantation unless otherwise specified. Race/ethnicity data was analyzed as reported by the implanting center.

**Statistical Analysis**

Summary statistics are presented as medians (inter quartile range [IQR]) or number (percent). Patient characteristics were compared using the chi-square test for categorical variables and the Kruskal-Wallis test for continuous variables. Time to death while on EXCOR® support, and time to transplant or recovery were analyzed as competing events. The non-parametric method of Anderson, Hansen, and Keiding¹⁰ was used to estimate the proportion still alive on support, dead while on support, transplanted, or removed for recovery. Because the distribution of deaths during support was not uniform, but rather peaked 7 days after VAD implant and then fell before slowly rising after 2 months (Supplement Figure 1), a multiphase non-proportional parametric model was used to characterize this pattern and perform multivariable analyses simultaneously for the hazard phases (early and late)¹¹. Variable selection for multivariable
analysis used the machine-learning technique of bagging (bootstrap aggregation)\textsuperscript{12-14}; 500 data sets were constructed by random sampling with replacement. Automated stepwise regression was performed with a $P$-value for retention of 0.05. Frequency of occurrence of individual risk factors or of clusters of related factors, such as rescaling transformations, was performed to identify those occurring in at least 50\% of analyses (the median rule, a measure of reliability, interpreted as the probability that a given factor has a true $P$-value $<0.05$).

Because an assumption of the model is that within each hazard phase there must be a linear relation between a continuous variable and the logarithm of the hazard ratio, each continuous variable was stratified by quintiles and plotted against the logarithm of the number of events divided by sum of follow-up time within each phase. If not linear, this suggested a family of transformations such as logarithmic and inverse on the one hand and squared or exponential on the other. These were generally scaled to the approximate mean of the variable to avoid arithmetic problems. The family of transformations was included in bootstrap variable selection. In the aggregation phase of bagging, we clustered these transformations of scale (including untransformed) and selected the representative most frequently occurring (exploring also whether more than one was frequently observed, suggesting a quadratic-type relationship). After main effects were identified by bagging, interactions suggested by investigators were formed, including those among pump size, congenital diagnosis, BIVAD support, and IDE study center. Using a fixed multivariable main effects model, these interactions were bagged in identical fashion as had been done for main effects. Sporadic missing values for variables ($<10\%$) were filled by 5-fold multiple imputation\textsuperscript{15} using a Markov Chain Monte Carlo technique. The aggregation of these 5 analyses (SAS PROC MIANALYXE) are reported\textsuperscript{16}. Analyses were performed using SAS version 9.1 and STATA version 10.0.
Results

Study Cohort

During the 4-year study period, 204 children were enrolled in the Berlin Heart EXCOR® trial database: 203 in the US, one in Canada. Of these, 68 met IDE trial criteria [48 (24%) who were in the original FDA IDE trial cohort and 20 additional patients who were implanted after trial enrollment was complete under a continued access protocol (CAP)]. One hundred thirty-six patients (67%) were implanted under compassionate-use, including 95 (70%) who received the EXCOR® at one of 27 centers not participating in the trial and 41 (30%) who met at least one clinical exclusion criteria at an IDE center. Baseline characteristics of the study cohort are summarized in Table 1. Overall, compassionate use patients were more likely to be younger, smaller, have CHD, be supported on ECMO, have worse end-organ function, and receive the smallest 10 milliliter pump.

Patient Survival

Survival at 12 months on EXCOR® support was 75%, including 64% who survived to transplant, 6% who recovered (device explanted and patient survived 30 days), and 5% alive with the device in place, while mortality on support was 25% (Figure 1A). Compared to IDE subjects, children implanted under compassionate use were less likely to reach transplant (53% versus 85%) and were more likely to die (34% versus 7%, P<0.01) (Figure 1). Table 2 summarizes the univariate predictors of death on EXCOR® support.

Early mortality on EXCOR® support was independently associated with lower body weight (Supplement Figure 2), higher bilirubin (Supplement Figure 3), and BIVAD support (Table 3). Late mortality was associated with bilirubin extremes (Supplement Figure 3), and a
reduced GFR for age, the strongest predictor overall. **Figure 2** summarizes the unadjusted effect of each variable on outcome depicted as categorical variables (see **Supplement Figures 2 and 3** for weight and bilirubin depicted as continuous variables). Among 33 infants <5 kg, 21 (64%) died including 42% (8/19) of those with CMP, and 93% (13/14) with CHD. Younger age and smaller pump size were also predictors of mortality, but were collinear with weight, which was preferred in the final model because of improved model reliability. Interaction terms for age, LVAD versus BIVAD support, cardiac diagnosis, pump size, IDE center status, and center volume were evaluated and were either non-significant or found not to improve model performance.

**Adverse Events and Cause of death**

The leading cause of death for the 51 patients who died on EXCOR® support was a neurological insult, which occurred in 17 (33%) patients who died (**Table 4**). Thromboembolic strokes causing death outnumbered hemorrhagic strokes by more than two to one. Respiratory failure, bleeding, and multi-system organ failure were the next most common causes. One patient death, at a non-IDE site, was adjudicated as a device malfunction (inadvertent cannula extraction while playing). **Table 5** summarizes the overall frequency of adverse events in the IDE and compassionate-use cohorts, which were similar. Of those with stroke severity data available (primary IDE cohort), 13% (N=6) were categorized as severe or fatal, 4% (N=2) as moderate, and 13% (N=6) as mild or no deficit.

**Figure 3** shows the growth in EXCOR® utilization in North America over the past decade, and the sharply reduced mortality observed at centers with a higher number of EXCOR® implants performed cumulatively at each center. Although the association between center volume and mortality was highly significant in the univariate analysis, it was non-significant.
after adjusting for other baseline characteristics.

**Discussion**

In this study, we found that among all 204 children supported with the Berlin Heart EXCOR® Pediatric VAD in the US during the current era, 75% survived to heart transplant or recovery. Twenty-five percent of children died, however the risk of death was not uniform for all children but varied significantly according to patient characteristics at EXCOR® implant. Smaller patient size, decreased renal function, total bilirubin, and biventricular support were associated with death on EXCOR® support whereas ECMO at implant and CHD were not. Neurological dysfunction occurred in 29% of children and was the leading cause of death.

Previous studies have reported widely divergent estimates of the EXCOR’s benefit and safety profile, with mortality ranging from 0 to 45% and stroke ranging from 11% to 45%5, 6, 17-23. The wide variability in risk estimates stems from limitations of earlier studies including small sample size18, 19, 22, 24, or single-institution experiences6, 24, 25, which has made it difficult for clinicians to know precisely when to offer EXCOR® support to their patients, or to provide families with contemporary risk-benefit data. Prior studies have also generally lacked objective clinical criteria for VAD implantation6, 25, or a standardized device treatment protocol6, 25— with uniform adverse event definitions, anticoagulation guidelines, and algorithm for pursuing BIVAD support—thus precluding the ability to know whether adverse events are related to the device itself or differences in patient management. Moreover, studies have tended to pool bridge-to-transplant and bridge-to-recovery patients6, 25, making it difficult to interpret transplant success rates. By contrast, the present report, which includes over 200 US children, represents by far the largest cohort of children supported with the EXCOR® to date, is limited to children
supported exclusively for the indication of bridge-to-heart transplant who were treated using a
standardized prospective treatment protocol within the current era. This study is the first to
demonstrate (1) the critical impact of end-organ dysfunction at implant on EXCOR® survival,
(2) that smaller patient weight is an independent risk factor for mortality, (3) the risk of
neurological events (29%) is relatively constant across diverse patient groups, and (4) the strong
univariate association between center volume and the risk of mortality (Figure 3).

The single most important predictor of patient mortality on EXCOR® support was the
degree of end-organ dysfunction—specifically renal and hepatic dysfunction—at the time of
VAD implant. Previous pediatric VAD studies have found no clear association between renal
function and mortality, in part because of how renal function was analyzed in previous models
(i.e. where the serum creatinine or creatinine clearance without adjustment for pediatric age were
used)5, 6. By using GFR categories adjusted for age9, renal function was found not only to be
statistically significant, but the single strongest term in the model. The mortality hazard related
to total bilirubin was less pronounced but more intricate, conferring risk at both low and high
bilirubin values (Table 3). Further research is needed to understand the relationship between
bilirubin and mortality.

Smaller infants were at higher risk of mortality where in this series nearly two-thirds of
infants <5 kg died. It is unclear why smaller infants face a higher risk of death but may be
related to a variety of factors including cardiac diagnosis, patient selection, post-cardiotomy
support, smaller pump size or anatomic structures, age-related differences in hemostasis—or
simply the challenge inherent in supporting blood flow at slower flow rates through miniaturized
components for prolonged time periods. Because of collinearity between weight, age, and pump
size, it is difficult to say with certainty which factor(s) is primarily responsible for the risk. A
variety of analytic strategies were used to isolate the primary factors where a transformation of
the “patient weight” variable appeared to create the model with the highest reliability. Further
analysis of infant EXCOR® outcomes is warranted. While survival for EXCOR patients is
clearly superior to ECMO for children over 5 kilograms, a survival advantage is more difficult to
demonstrate in children under 5 kilograms based on the published ECMO experience³,¹⁸,¹⁹,
although individual center experiences may vary.”

BIVAD support was also associated with mortality, a consistent risk factor for death in
the adult VAD experience²⁶,²⁷ and the report by Morales⁵. Whether the risks associated with
BIVAD use are attributable to the devices themselves, or that patients implanted with BIVADs
tend to be sicker as demonstrated in adults²⁶ (perhaps because of delayed device implant)—or
both is unclear. Programs have documented that as experience grows and patient selection
matures, BIVAD use tends to decrease and that this is associated with a decrease in mortality.

Death occurred more frequently in children with CHD, on ECMO pre-implant, at non-
IDE centers, and at centers with a lower EXCOR® patient volume, but these differences were
not statistically significant after adjusting for other factors. While children with CHD and those
requiring ECMO remain readily identifiable risk groups, our findings suggest that their higher
mortality is driven primarily by differences in patient size, end-organ dysfunction and use of
BIVAD support, rather than either CHD or ECMO per se. Indeed, while our data suggest that
ECMO should be generally viewed to increase the risk of VAD support in most children, it is
possible that ECMO, when used strictly for short-term resuscitative support to normalize end-
organ function immediately prior to VAD implant, may improve VAD candidacy in selected
patients. This duality of effect for ECMO on mortality may account for its absence in the final
multivariable model.” Similarly, and perhaps more noteworthy for its absence in the model, is
the strong univariable effect of center EXCOR® volume on patient mortality (Figure 3). Its absence suggests that the sharply lower patient mortality observed at centers implanting more devices may be best explained by experienced centers learning to implant the device in less sick patients over time, rather than other factors.

Neurological dysfunction, which occurred in 29% of EXCOR® recipients, was the leading cause of death. While the observed risk in the present study is higher than the prevalence reported for adult continuous flow LVADs, EXCOR® recipients were considerably sicker than adult patients in these series. Moreover, the magnitude of the risk in EXCOR® recipients is not appreciably different from first-generation adult pulsatile pumps used in the 1990s. Nevertheless, because of this and other factors, selected pediatric centers are expressing some preference to use adult continuous-flow VADs in their larger pediatric patients who may be eligible for both devices. However it is important to note that pediatric-specific adverse event data for adult continuous-flow devices are still relatively limited.” Interestingly, most strokes in the present study were thromboembolic, rather than hemorrhagic, which may carry implications for refining further the anticoagulation balance point in future iterations of the anti-thrombotic protocol.

The findings of this study have several implications. First, our findings suggest that, for the very first time in the US, ventricular assist device therapy has emerged as a new standard of care for bridging children to transplant when optimal medical therapy failed. The relatively rapid adoption of this technology by more than 45 centers in the US and Canada—in a relatively short timeframe—likely stems from widespread appreciation of the unacceptably high waiting list mortality in US infants and children with or without ECMO, the lack of alternative devices, the favorable German EXCOR® experience, and a foundational shift in the
willingness of US clinicians to use emerging circulatory support technologies which have been variably used in Germany as early as the mid-1990s\textsuperscript{3,33-37}. This fundamental change in US clinical practice represents a major milestone for the field of pediatric heart failure therapy. With a growing number of novel miniaturized pediatric VADs now on the horizon\textsuperscript{38-40}, FDA approval of the EXCOR\textsuperscript{®} marks the beginning of a new era in pediatric mechanical circulatory support.

Second, our findings suggest that while the very best EXCOR\textsuperscript{®} results can be achieved in children who met the FDA trial inclusion criteria, the EXCOR\textsuperscript{®} can also provide life-saving support to children with a broader variety of heart failure syndromes, as reflected in the compassionate-use subjects. To be sure, because of the large amount of data collected by the Sponsor in the compassionate-use registry, the FDA took the unusual step of expanding the indications for EXCOR\textsuperscript{®} approval beyond the original trial inclusion criteria—granting it to essentially all “pediatric candidates with severe isolated left ventricular or biventricular dysfunction who are candidates for cardiac transplant and require circulatory support.”\textsuperscript{41}

While including a compassionate-use registry in the study design is costly, it provided a valuable mechanism to capture device performance data on subjects who fail to meet rigid inclusion criteria, which tends to happen frequently in pediatrics because of the heterogeneity of the patient population.\textsuperscript{42}

Lastly, and perhaps most importantly, our findings suggest that the single most effective way for centers to improve patient outcomes on EXCOR\textsuperscript{®} support is to devote careful attention to patient selection. Data from the present study provide important evidence to support what many have long suspect: that waiting too long to implant a device—such that renal, hepatic and/or right ventricular function have deteriorated significantly—sharply increases the risk of death on EXCOR\textsuperscript{®} support. Equally important, however, is for centers to exercise caution in
initiating VAD support too early (i.e. when a child’s heart failure might still be managed effectively with further adjustments to medical therapy) thus exposing children unnecessarily to the risks of VAD support like stroke, bleeding and infection.

This study must be interpreted within the context of the retrospective study design. First, the present study could be susceptible to selection bias especially if a non-random sample of subjects was ascertained for analysis. However, because the present analysis captured essentially all cases during the study period, it is unlikely that selection bias played a major role in the study’s findings. Second, this risk factor analysis was limited to variables recorded at the time of device implant and did not account for post-implant time-varying hazards (e.g. anticoagulant levels) that may be associated with adverse outcome. Future studies are warranted to examine post-implant factors associated with outcome. Lastly, a small number of neurological events, such as global ischemic encephalopathy, covert/asymptomatic stroke and post-operative seizure were not captured using the INTERMACS definition for neurological dysfunction used in the IDE trial.

In summary, the Berlin Heart EXCOR® Pediatric Ventricular Assist Device has emerged as a new standard of care for children requiring mechanical support as a bridge to heart transplant. FDA approval of the EXCOR®—the first pediatric-specific VAD to receive FDA approval and to be widely accepted in the US—represents a major milestone for children with advanced heart failure. Seventy-five percent of children survived to transplant or recovery with 29% experiencing some type of neurological dysfunction. The single most effective way to improve patient outcomes on EXCOR® support, especially in the smallest patients, is to choose candidates carefully—ideally once failure of medical therapy has been established, but before the onset of significant end-organ dysfunction, including right heart failure necessitating right
ventricular assist device (RVAD) support. Further efforts to improve the safety and survival of children supported with the EXCOR® or through the development of the next generation of pediatric VADs, will likely lead to a reduction in the frequency and severity of terminal heart failure, which for too many children, remains a highly fatal condition.

**Funding Sources:** The Berlin Heart IDE study was supported by Berlin Heart, Inc. and by a grant from the FDA’s Office of Orphan Product Development (R01-FD03357, PI Dr. Almond, Mr. Kroslowitz). Dr. Almond was supported by the Alexia Clinton Family and the Heart Failure/Transplant Education Fund.

**Conflict of Interest Disclosures:** Mr. Robert Kroslowitz and Ms. Christine Tjossem are employees of Berlin Heart. Dr. Holger Buchholz reports being on an advisory board and receiving consultancy fees from Levitronix. Dr. Tilman Humpl reports receiving payments for lectures and/or service on speakers bureaus from Berlin Heart, Inc. Dr. Patricia Massicotte reports receiving consultancy fees from Bayer, Levitronix and Sanofi Aventis. Dr. Lori Jordan reports receiving consultancy fees and being on an Advisory Board for Berlin Heart, Inc.

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41. U.S. Food and drug administration (h100004) approval of the berlin heart excor pediatric ventricular assist device. 

Table 1. Baseline characteristics of the patients according to cohort.

<table>
<thead>
<tr>
<th>Demographic</th>
<th>TOTAL N=204</th>
<th>IDE Criteria Cohort N=68</th>
<th>Compassionate Use Cohort N=136</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr), median (IQR)</td>
<td>1.6 [0.5, 5.4]</td>
<td>2.1 [0.6, 7.1]</td>
<td>1.4 [0.4, 4.4]</td>
<td>0.03</td>
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<tr>
<td>Weight (kg), median (IQR)</td>
<td>10.0 [6.5, 16.6]</td>
<td>12.1 [7.3, 22.2]</td>
<td>9.4 [5.7, 14.8]</td>
<td>0.01</td>
</tr>
<tr>
<td>Weight categories</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight &lt; 5 kg</td>
<td>33 (16.2%)</td>
<td>6 (8.8%)</td>
<td>27 (20.0%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Weight 5-10 kg</td>
<td>71 (34.8%)</td>
<td>22 (32.4%)</td>
<td>49 (36.0%)</td>
<td></td>
</tr>
<tr>
<td>Weight &gt; 10kg</td>
<td>100 (49.0%)</td>
<td>40 (58.8%)</td>
<td>60 (44.1%)</td>
<td></td>
</tr>
<tr>
<td>BSA (m²), median (IQR)</td>
<td>0.48 [0.35, 0.72]</td>
<td>0.53 [0.38, 0.88]</td>
<td>0.45 [0.32, 0.64]</td>
<td>0.02</td>
</tr>
<tr>
<td>Female gender</td>
<td>97 (47.6%)</td>
<td>34 (50.0%)</td>
<td>63 (46.3%)</td>
<td>0.62</td>
</tr>
<tr>
<td>Non-white race</td>
<td>74/198 (37.4%)</td>
<td>26 (38.2%)</td>
<td>48 (36.9%)</td>
<td>0.86</td>
</tr>
<tr>
<td>Congenital Heart Disease</td>
<td>59 (28.9%)</td>
<td>10 (14.7%)</td>
<td>49 (36.0%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Single Ventricle</td>
<td>19 (9.3%)</td>
<td>0 (0.0%)</td>
<td>19 (14.0%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hemodynamic Support</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECMO</td>
<td>83 (40.7%)</td>
<td>18 (26.5%)</td>
<td>65 (47.8%)</td>
<td>0.005</td>
</tr>
<tr>
<td>Ventilator</td>
<td>74 (36.3%)</td>
<td>27 (39.7%)</td>
<td>47 (34.6%)</td>
<td></td>
</tr>
<tr>
<td>Other support/no support</td>
<td>47 (23.4%)</td>
<td>23 (33.8%)</td>
<td>24 (17.7%)</td>
<td></td>
</tr>
<tr>
<td>INTERMACS® profile 1</td>
<td>107 (52.5%)</td>
<td>30 (44.1%)</td>
<td>77 (56.6%)</td>
<td>0.092</td>
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<tr>
<td>INTERMACS® profile 2</td>
<td>90 (44.1%)</td>
<td>38 (55.9%)</td>
<td>52 (38.2%)</td>
<td>0.017</td>
</tr>
<tr>
<td>Serum Cr (mg/dL), median(IQR)</td>
<td>0.4 [0.3, 0.6]</td>
<td>0.4 [0.3, 0.6]</td>
<td>0.5 [0.3, 0.7]</td>
<td>0.20</td>
</tr>
<tr>
<td>GFR median (IQR)</td>
<td>102 [63, 154]</td>
<td>115 [84, 160]</td>
<td>89 [59, 151]</td>
<td>0.019</td>
</tr>
<tr>
<td>GFR categories (age adjusted)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30% predicted</td>
<td>11 (5.4%)</td>
<td>0 (0.0%)</td>
<td>11 (8.1%)</td>
<td>0.017</td>
</tr>
<tr>
<td>30-99% predicted</td>
<td>43 (21.1%)</td>
<td>11 (16.2%)</td>
<td>32 (23.5%)</td>
<td></td>
</tr>
<tr>
<td>&gt;99% predicted</td>
<td>150 (73.5%)</td>
<td>57 (83.8%)</td>
<td>93 (68.4%)</td>
<td></td>
</tr>
<tr>
<td>Bilirubin (mg/dL), median (IQR)</td>
<td>1.0 [0.5, 2.2]</td>
<td>0.8 [0.5, 1.5]</td>
<td>1.1 [0.6, 2.4]</td>
<td>0.03</td>
</tr>
<tr>
<td>&lt;0.6</td>
<td>53/194 (27.3%)</td>
<td>22/67 (32.8%)</td>
<td>31/127 (24.4%)</td>
<td></td>
</tr>
<tr>
<td>0.7-1.2</td>
<td>55/194 (28.4%)</td>
<td>22/67 (32.8%)</td>
<td>33/127 (26.0%)</td>
<td>0.12</td>
</tr>
<tr>
<td>&gt;1.2</td>
<td>86/194 (44.7%)</td>
<td>23/67 (243%)</td>
<td>63/127 (49.6%)</td>
<td></td>
</tr>
<tr>
<td>EXCOR® Pump Size</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 milliliters</td>
<td>76 (37.3%)</td>
<td>19 (27.9%)</td>
<td>57 (41.9%)</td>
<td>0.04</td>
</tr>
<tr>
<td>25/30 milliliters</td>
<td>103 (50.5%)</td>
<td>36 (52.9%)</td>
<td>67 (49.3%)</td>
<td></td>
</tr>
<tr>
<td>50/60 milliliters</td>
<td>25 (12.3%)</td>
<td>13 (19.1%)</td>
<td>12 (8.8%)</td>
<td></td>
</tr>
<tr>
<td>Device Type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVAD</td>
<td>129 (63.2%)</td>
<td>42 (61.8%)</td>
<td>87 (64.0%)</td>
<td>0.76</td>
</tr>
<tr>
<td>BVAD</td>
<td>75 (36.8%)</td>
<td>26 (38.2%)</td>
<td>49 (36.0%)</td>
<td></td>
</tr>
<tr>
<td>ECMO duration &gt;10 days prior to VAD</td>
<td>19 (9.3%)</td>
<td>0 (0.0%)</td>
<td>19 (14.0%)</td>
<td>-----</td>
</tr>
<tr>
<td>Total EXCOR® implants per center</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-5 implants</td>
<td>51 (25.0%)</td>
<td>3 (4.4%)</td>
<td>48 (35.3%)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>6-10 implants</td>
<td>61 (29.9%)</td>
<td>7 (10.3%)</td>
<td>54 (39.7%)</td>
<td></td>
</tr>
<tr>
<td>&gt;10 implants</td>
<td>92 (45.1%)</td>
<td>58 (85.3%)</td>
<td>34 (25.0%)</td>
<td></td>
</tr>
</tbody>
</table>

IDE, investigational device exemption cohort; BSA, body-surface area (m²); ECMO, extra-corporeal membrane oxygenation; INTERMACS, Inter-agency Registry for Mechanically Assisted Circulatory Support; GFR, glomerular filtration rate (ml/min/1.73m²) estimated using the Schwartz formula; LVAD, left ventricular assist device; BIVAD, biventricular assist device; CPR, cardiopulmonary resuscitation. Categorical variables were compared using the Chi-square test unless otherwise noted with an "*", where the Fisher Exact Test was used.
Table 2. Univariable factors associated with early and late mortality.

<table>
<thead>
<tr>
<th></th>
<th>Overall Mortality</th>
<th>Early Mortality (≤ 2 months) N=42/204</th>
<th>Late Mortality (&gt; 2 months) N=9/204</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=51/204</td>
<td>N % Died P</td>
<td>N % Died P</td>
<td>N % Died P</td>
</tr>
<tr>
<td>Weight (kg) categories</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight &lt; 5 kg</td>
<td>33 64% &lt;0.001</td>
<td>33 64% &lt;0.001</td>
<td>33 0% 0.5*</td>
</tr>
<tr>
<td>Weight 5-10 kg</td>
<td>71 23%</td>
<td>71 17%</td>
<td>71 6%</td>
</tr>
<tr>
<td>Weight &gt; 10kg</td>
<td>100 14%</td>
<td>100 9%</td>
<td>100 5%</td>
</tr>
<tr>
<td>Female gender</td>
<td>97 28% 0.4</td>
<td>97 25% 0.2</td>
<td>97 3% 0.5*</td>
</tr>
<tr>
<td>Non-white race</td>
<td>74 19% 0.1</td>
<td>74 15% 0.1</td>
<td>74 4% 1.0*</td>
</tr>
<tr>
<td>Hemodynamic Support</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECMO</td>
<td>83 34%</td>
<td>83 30%</td>
<td>83 4%</td>
</tr>
<tr>
<td>Ventilator</td>
<td>74 19%</td>
<td>74 16%</td>
<td>74 3%</td>
</tr>
<tr>
<td>Neither</td>
<td>47 19%</td>
<td>47 11%</td>
<td>47 9%</td>
</tr>
<tr>
<td>INTERMACS® profile 1</td>
<td>107 31% 0.04</td>
<td>107 29% 0.002</td>
<td>107 2% 0.09*</td>
</tr>
<tr>
<td>INTERMACS® profile 2</td>
<td>90 18% 0.03</td>
<td>90 11% 0.003</td>
<td>90 7% 0.2*</td>
</tr>
<tr>
<td>GFR categories</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30% predicted</td>
<td>11 82%</td>
<td>11 73%</td>
<td>11 9%</td>
</tr>
<tr>
<td>30-99% predicted</td>
<td>43 37%</td>
<td>43 33%</td>
<td>43 5%</td>
</tr>
<tr>
<td>&gt;99% predicted</td>
<td>150 17%</td>
<td>150 13%</td>
<td>150 4%</td>
</tr>
<tr>
<td>Total bilirubin (mg/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;0.6</td>
<td>53 13%</td>
<td>53 9%</td>
<td>53 4%</td>
</tr>
<tr>
<td>0.7-1.2</td>
<td>55 16%</td>
<td>55 11%</td>
<td>55 5%</td>
</tr>
<tr>
<td>&gt;1.2</td>
<td>86 40%</td>
<td>86 36%</td>
<td>86 3%</td>
</tr>
<tr>
<td>Cardiac Diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>145 16%</td>
<td>145 12%</td>
<td>145 3%</td>
</tr>
<tr>
<td>Dilated CM</td>
<td>110 15%</td>
<td>110 11%</td>
<td>110 4%</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>28 14%</td>
<td>28 11%</td>
<td>28 4%</td>
</tr>
<tr>
<td>Restrictive CM</td>
<td>4 25%</td>
<td>4 25%</td>
<td>4 0%</td>
</tr>
<tr>
<td>Other CM</td>
<td>3 67%</td>
<td>3 67%</td>
<td>3 0%</td>
</tr>
<tr>
<td>CHD</td>
<td>59 47%</td>
<td>59 41%</td>
<td>59 7%</td>
</tr>
<tr>
<td>2-ventricle</td>
<td>40 50%</td>
<td>40 45%</td>
<td>40 5%</td>
</tr>
<tr>
<td>1-ventricle</td>
<td>19 42%</td>
<td>19 32%</td>
<td>19 10%</td>
</tr>
<tr>
<td>Device Type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVAD</td>
<td>129 22%</td>
<td>129 16%</td>
<td>129 6%</td>
</tr>
<tr>
<td>BVAD</td>
<td>75 29%</td>
<td>75 28%</td>
<td>75 1%</td>
</tr>
<tr>
<td>ECMO &gt;10 days</td>
<td>19 32% 0.6*</td>
<td>19 26% 0.6*</td>
<td>19 5% 0.6*</td>
</tr>
<tr>
<td>CPR within 48 hours prior to VAD implantation</td>
<td>8 13% 0.7*</td>
<td>8 12% 1.0*</td>
<td>8 0% 1.0*</td>
</tr>
<tr>
<td>Infection at implant</td>
<td>10 40% 0.3*</td>
<td>10 30% 0.4*</td>
<td>10 10% 0.4*</td>
</tr>
</tbody>
</table>

ECMO, extra-corporeal membrane oxygenation; INTERMACS, Inter-agency Registry for Mechanically Assisted Circulatory Support; GFR, glomerular filtration rate (ml/min/1.73m²) estimated using the Schwartz formula; CHD, congenital heart disease; LVAD, left ventricular assist device, BIVAD, biventricular assist device; CPR, cardiopulmonary resuscitation. Categorical variables were compared using the Chi-square test unless otherwise noted with an "*", where the Fisher Exact Test was used.
Table 3. Risk factors for death on EXCOR® support

<table>
<thead>
<tr>
<th>Factor</th>
<th>Coefficient ± SD</th>
<th>P</th>
<th>Reliability (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Early mortality (within 2 months)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower patient weight at implant (Kg) †</td>
<td>0.12 ± 0.021</td>
<td>&lt;.0001</td>
<td>54</td>
</tr>
<tr>
<td>Higher serum total Bilirubin (mg/dL) ‡</td>
<td>0.42 ± 0.16</td>
<td>.008</td>
<td>52</td>
</tr>
<tr>
<td>Biventricular assist device</td>
<td>0.98 ± 0.36</td>
<td>.006</td>
<td>50</td>
</tr>
<tr>
<td><strong>Late mortality (beyond 2 months)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Higher serum total Bilirubin (mg/dL)</td>
<td>0.41 ± 0.11</td>
<td>.0003</td>
<td>71</td>
</tr>
<tr>
<td>Lower total Bilirubin (mg/dL) §</td>
<td>0.086 ± 0.019</td>
<td>&lt;.0001</td>
<td>71</td>
</tr>
<tr>
<td>GFR for age below normal</td>
<td>2.08 ± 0.81</td>
<td>.01</td>
<td>55</td>
</tr>
</tbody>
</table>

* Percent of times factor occurred in 500 bootstrapped models.
†. [INV(Weight/15)]², inverse transformation
‡. LOG(Bilirubin), logarithmic transformation.
§. [INV(Bilirubin)]², inverse squared transformation
GFR was estimated using the Schwartz formula

Table 4. Cause of death for children who died on EXCOR support (N=51)

<table>
<thead>
<tr>
<th>Factor</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurological Injury</td>
<td>17</td>
<td>33%</td>
</tr>
<tr>
<td>Thromboembolic</td>
<td>12</td>
<td>24%</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>5</td>
<td>10%</td>
</tr>
<tr>
<td>Respiratory Failure</td>
<td>6</td>
<td>50%</td>
</tr>
<tr>
<td>Bleeding</td>
<td>3</td>
<td>6%</td>
</tr>
<tr>
<td>Multi-system organ failure</td>
<td>3</td>
<td>6%</td>
</tr>
<tr>
<td>Right ventricular failure</td>
<td>3</td>
<td>6%</td>
</tr>
<tr>
<td>Low-cardiac output syndrome</td>
<td>2</td>
<td>4%</td>
</tr>
<tr>
<td>Systemic thromboembolism</td>
<td>2</td>
<td>4%</td>
</tr>
<tr>
<td>Renal failure</td>
<td>1</td>
<td>2%</td>
</tr>
<tr>
<td>Device Malfunction</td>
<td>1</td>
<td>2%</td>
</tr>
<tr>
<td>Other*</td>
<td>2</td>
<td>4%</td>
</tr>
</tbody>
</table>

*2 patient deaths occurred within 30 days of EXCOR explantation, one from heart failure, one from RV rupture early after heart transplant.
Table 5. Serious Adverse Event Summary*  

<table>
<thead>
<tr>
<th>Event</th>
<th>Overall Cohort (N=204)</th>
<th>IDE Criteria Subjects (N=68)</th>
<th>Compassionate Use Subjects (N=136)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>% of pts</td>
<td>Rate †</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>162</td>
<td>44%</td>
<td>1.2</td>
</tr>
<tr>
<td>Cardiac Arrhythmia</td>
<td>24</td>
<td>9%</td>
<td>0.2</td>
</tr>
<tr>
<td>Hemolysis</td>
<td>7</td>
<td>3%</td>
<td>0.1</td>
</tr>
<tr>
<td>Hepatic Dysfunction</td>
<td>26</td>
<td>9%</td>
<td>0.2</td>
</tr>
<tr>
<td>Major Infection</td>
<td>200</td>
<td>46%</td>
<td>1.5</td>
</tr>
<tr>
<td>Neurological Dysfunction</td>
<td>74</td>
<td>29%</td>
<td>0.5</td>
</tr>
<tr>
<td>Type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thromboembolic</td>
<td>47</td>
<td>21%</td>
<td>0.3</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>5</td>
<td>2%</td>
<td>0.0</td>
</tr>
<tr>
<td>Severity ‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild/no symptoms</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Moderate</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Severe/Fatal</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Renal Dysfunction</td>
<td>28</td>
<td>12%</td>
<td>0.2</td>
</tr>
<tr>
<td>Respiratory Failure</td>
<td>76</td>
<td>29%</td>
<td>0.6</td>
</tr>
<tr>
<td>Right Heart Failure</td>
<td>28</td>
<td>12%</td>
<td>0.2</td>
</tr>
<tr>
<td>Arterial Non-CNS Thromboembolism</td>
<td>7</td>
<td>3%</td>
<td>0.1</td>
</tr>
<tr>
<td>Other §</td>
<td>78</td>
<td>26%</td>
<td>0.6</td>
</tr>
</tbody>
</table>

*Adverse events were defined according to pediatric-specific criteria adapted from INTERMACS, unless otherwise noted*.
†Total number of events per 100 days of mechanical support.
‡The severity of neurological deficits was defined using the Pediatric Stroke Outcome Measure at last follow-up and available for the 48 original IDE subjects only totaling 2,787 days of support. Scores between 0 and 1 were categorized as none/mild, between 1.5 and 2 categorized as moderate, and ≥2.5 or resulting in withdrawal of support categorized as severe.
Non-IDE study sites were not required to have a PSOM performed, which accounts for the missing data.
§Among 78 other serious adverse events reported were global ischemic encephalopathy (N=2), seizures (N=3) and subdural hematomas (N=2).
Figure Legends:

**Figure 1.** Competing outcomes for waitlisted children supported with the EXCOR® as a bridge to transplant through 12 months. **Panel A:** Competing outcomes for the overall cohort during EXCOR® support (N=204). **Panel B:** Competing outcomes for the IDE cohort during EXCOR® support (N=68). **Panel C:** Competing outcomes for the compassionate-use cohort during EXCOR® support (N=136).

**Figure 2.** Survival for children supported with the Berlin Heart EXCOR® Pediatric as a bridge-to-transplant according. **Panel A:** Effect of patient weight at EXCOR® implant on survival. **Panel B:** Effect of EXCOR® support type on survival. **Panel C:** Effect of GFR adjusted for age on survival during EXCOR® support. **Panel D:** Effect of serum total bilirubin at EXCOR® implant on survival.

**Figure 3.** **Panel A:** Growth in utilization of the Berlin Heart EXCOR® Pediatric VAD in North America over the past decade. **Panel B:** Association between center volume and mortality in the overall cohort (P<0.001). The difference was not statistically significant after adjusting for patient characteristics at the time of device implant.
Overall Cohort (N=204)

- Transplant: 64%
- Death: 25%
- Explanted: 6%
- Alive (device in place): 5%

Figure 1A
Figure 1B

- Transplant: 85%
- Death: 7%
- Alive (device in place): 4%
- Explanted: 3%

% of Patients vs. Months Post Implant
Figure 1C
Figure 2B
Figure 2C
Figure 3A
Figure 3B

<table>
<thead>
<tr>
<th>Implants</th>
<th>Percent Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-5</td>
<td>47%</td>
</tr>
<tr>
<td>6-10</td>
<td>28%</td>
</tr>
<tr>
<td>&gt;10</td>
<td>11%</td>
</tr>
</tbody>
</table>
The Berlin Heart EXCOR® Pediatric Ventricular Assist Device for Bridge to Heart Transplantation in US Children


Circulation. published online March 28, 2013;

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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## SUPPLEMENTAL TABLE 1. Inclusion/exclusion criteria for the Berlin Heart EXCOR IDE clinical study.

### Inclusion Criteria
1. Severe NYHA Functional Class IV (or Ross Functional Class IV for subjects ≤ 6 years) heart failure refractory to optimal medical therapy, and has met at least one of the following criteria:
   a. INTERMACS profile status 1 or 1A, i.e. critical cardiogenic shock (low BP unresponsive to support, compromised end organ perfusion, < 24 hour survival expected without mechanical support; may be due to VT/VF (1A))
   b. INTERMACS™ profile status 2 or 2A (i.e. progressive decline): not in imminent danger, but worsening despite optimal inotropic therapy; may be due to VT/VF (2A) AND at least one of the following criteria
      i. Decline in renal function as defined by a 50% reduction in estimated GFR despite optimization of subject volume status
      ii. Decline in nutritional status as defined by a sustained (≥7 days) inability to tolerate an enteral nutritional intake sufficient to provide at least 75% of the prescribed caloric needs for the subject, or signs of nutritional compromise (cachexia, nutritional weight loss) despite appropriate intervention
      iii. Decline in mobility/ambulation as defined by sustained bed confinement (≥7 days without prospect for improvement) attributable to heart failure symptoms or its treatment (e.g. intubation for pulmonary edema)
   c. Support with extra-corporeal membrane oxygenation (ECMO) or other mechanical circulatory support device
   OR
   d. Unable to separate from cardiopulmonary bypass (must be listed for heart transplantation at time of transfer to the operating room)
2. Listed (UNOS status 1A or equivalent) for cardiac transplantation
3. Two-ventricle circulation, including cardiomyopathy, repaired structural heart disease (e.g. ALCAPA, aortic stenosis) or acquired heart disease (e.g. myocarditis, Kawasaki disease)
4. Age 0 to 16 years; corrected gestational (CGA) at least 37 weeks
5. Weight ≥ 3 kg and ≤ 60 kg
6. Legal guardian (and subject if age-appropriate) understands the nature of the procedure, are willing to comply with associated follow-up evaluations, and provide written informed consent and assent prior to the procedure

### Exclusion Criteria
1. Support on ECMO for ≥10 days
2. Cardiopulmonary resuscitation (CPR) duration ≥30 minutes within 48 hours prior to device implantation
3. Body weight < 3.0 kg or BSA > 1.5 m²
4. Presence of mechanical aortic valve
5. Unfavorable or technically-challenging cardiac anatomy including single ventricle lesions, complex heterotaxy, and restrictive cardiomyopathy
6. Evidence of intrinsic hepatic disease as defined by a total bilirubin level or AST/ALT greater than five times the upper limit of normal for age, except in association with acute heart failure as determined by the principal investigator
7. Evidence of intrinsic renal disease as defined by a serum creatinine greater than 3 times the upper limit of normal for age, except in association with acute heart failure as determined by the principal investigator
8. Hemodialysis or peritoneal dialysis (not including dialysis or Continuous Veno-Venous Hemofiltration (CVVH) for volume removal)
9. Evidence of intrinsic pulmonary disease (e.g. chronic lung disease, RDS) as defined by need for chronic mechanical ventilation, except in association with acute heart failure as determined by the principal investigator
10. Moderate or severe aortic and/or pulmonic valve insufficiency considered technically challenging to repair at the time of the device implantation as determined by the principal investigator
11. Apical VSD or other hemodynamically-significant lesion considered technically challenging to repair at the time of device implantation as determined by the principal investigator
12. Documented heparin induced thrombocytopenia (HIT) or idiopathic thrombocytopenia purpura (ITP) or other contraindication to anticoagulant/antiplatelet therapy
13. Documented coagulopathy (e.g. Factor VIII deficiency, disseminated intravascular coagulation) or thrombophilic disorder (e.g. Factor V Leiden mutation)
14. Hematologic disorder causing fragility of blood cells or hemolysis (e.g. sickle cell disease)
15. Active infection within 48 hours of implant demonstrated by:
   a. Positive blood culture
   OR
   b. Temperature >38 degrees C and WBC >15,000/ ml
16. Documented human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS)
17. Evidence of recent or life-limiting malignant disease
18. Stroke within past 30 days prior to enrollment, or congenital CNS malformation syndrome associated with increased risk of bleeding (e.g. arteriovenous malformation, moya moya)
19. Psychiatric or behavioral disease (e.g. antisocial disorder) with a high likelihood for non-compliance
20. Currently participating in another investigational device or drug trial and has not completed the required follow-up period for that study
21. Subject is pregnant or nursing
**SUPPLEMENTAL TABLE 2 – Adverse event definitions used in the trial (adapted from INTERMACS)**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major Bleeding</strong></td>
<td>An episode of internal or external bleeding that results in death, the need for re-operation or hospitalization; or necessitates transfusion of red blood cells as follows: Within any 24 hour period: 1. ≥ 4U packed red blood cells (PRBC) within any 24 hour period during the first 7 days post-implant 2. Any transfusion of packed red blood cells (PRBC) after 7 days following implant with the Investigator recording the number of units given. For subjects &lt; 50 kg: 1. ≥ 20cc/kg packed red blood cells (PRBC) within any 24 hour period during the first 7 days post-implant 2. Any transfusion of packed red blood cells (PRBC) after 7 days following implant with the Investigator recording the number of units given. <strong>NOTE:</strong> Hemorrhagic stroke is considered a neurological event and not as a separate bleeding event.</td>
</tr>
<tr>
<td><strong>Cardiac Arrhythmias</strong></td>
<td>Any documented arrhythmia that results in clinical compromise (e.g., diminished VAD flow, oliguria, pre-syncpe or syncpe) that requires hospitalization or occurs during a hospital stay. Cardiac arrhythmias are classified as 1 of 2 types: 1. Sustained ventricular arrhythmia requiring defibrillation or cardioversion. 2. Sustained supraventricular arrhythmia requiring drug treatment or cardioversion.</td>
</tr>
<tr>
<td><strong>Pericardial Fluid Collection</strong></td>
<td>Accumulation of fluid or clot in the pericardial space that requires surgical intervention or percutaneous catheter drainage. This event will be subdivided into those with clinical signs of tamponade (e.g. increased central venous pressure and decreased cardiac/VAD output) and those without signs of tamponade.</td>
</tr>
<tr>
<td><strong>Device Malfunction</strong></td>
<td>Device malfunction denotes a failure of one or more of the components of the EXCOR® Pediatric system which either directly causes or could potentially induce a state of inadequate circulatory support (low cardiac output state) or death. The manufacturer must confirm device failure. A failure that was iatrogenic or recipient-induced will be classified as an Iatrogenic/Recipient-Induced Failure. Device failure should be classified according to which components fails as follows: 1. Pump failure (blood contacting components of pump and any motor or other pump actuating mechanism that is housed with the blood contacting components). In the special situation of pump thrombosis, thrombus is documented to be present within the device or its conduits that result in or could potentially induce circulatory failure. <strong>Note:</strong> Blood pump replacement due to suspected thrombus is not included in this definition. 2. Non-pump failure (e.g., external pneumatic drive unit, electric power supply unit, batteries, controller, interconnect cable, compliance chamber) <strong>Note:</strong> Low cardiac output is defined as a multifaceted syndrome of persistent hypotension, inadequate tissue perfusion, oliguria and rising lactate that is clinically defined by an estimated CI less than 2.0 L/min/m² that is persisting for greater than 60 minutes despite optimization of medical therapy.</td>
</tr>
</tbody>
</table>
### SUPPLEMENTAL TABLE 2 – Adverse event definitions used in the trial (adapted from INTERMACS)

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<tr>
<td>Early Hemolysis</td>
<td>Early Hemolysis is defined by clinical signs associated with hemolysis (e.g. anemia, low hematocrit, hyperbilirubinemia) occurring within the first 72 hours post-implant. Hemolysis related to documented non-device-related causes (e.g. transfusion or drug) is excluded from this definition.</td>
</tr>
<tr>
<td>Hemolysis</td>
<td>A plasma-free hemoglobin value that is greater than 40 mg/dl, in association with clinical signs associated with hemolysis (e.g., anemia, low hematocrit, hyperbilirubinemia) occurring after the first 72 hours post-implant. Hemolysis related to documented non-device-related causes (e.g. transfusion or drug) is excluded from this definition.</td>
</tr>
</tbody>
</table>
| Hepatic Dysfunction    | An increase in any two of the following hepatic laboratory values  
  - total bilirubin  
  - aspartate aminotransferase/AST  
  - alanine aminotransferase/ALT  
  to a level greater than three times the upper limit of normal for the hospital, beyond 14 days post-implant (or if hepatic dysfunction is the primary cause of death). |
| Hypertension           | New onset blood pressure elevation greater than or equal to 140 mm Hg or 90 mm Hg diastolic. In subjects under 18 years of age weighing < 50 kg, hypertension is defined as systolic, diastolic, or mean blood pressure greater than the 95th percentile for age which requires the addition of iv or oral drug therapy for management. |
| Major Infection        | A clinical infection accompanied by pain, fever, drainage and/or leukocytosis that is treated by anti-microbial agents (non-prophylactic). A positive culture from the infected site or organ should be present unless strong clinical evidence indicates the need for treatment despite negative cultures. The general categories of infection are listed below:  

  **Localized Non-Device Infection**  
  Infection localized to any organ system or region (e.g. mediastinitis) without evidence of systemic involvement (see sepsis definition), ascertained by standard clinical methods and either associated with evidence of bacterial, viral, fungal or protozoal infection, and/or requiring empirical treatment.  

  **Percutaneous Site and/or Pocket Infection**  
  A positive culture from the skin and/or tissue surrounding the drive line or from the tissue surrounding the external housing of a pump implanted within the body, coupled with the need to treat with antimicrobial therapy, when there is clinical evidence of infection such as pain, fever, drainage, or leukocytosis.  

  **Internal Pump Component, Inflow or Outflow Tract Infection**  
  Infection of blood-contacting surfaces of the VAD documented by positive center culture. (There should be a separate data field for paracorporeal pump that describes infection at the percutaneous cannula center, e.g. Thoratec PVAD).  

  **Sepsis**  
  Evidence of systemic involvement by infection, manifested by positive blood cultures and/or hypotension. |
| Myocardial Infarction   | Two categories of myocardial infarction will be identified: |
### SUPPLEMENTAL TABLE 2 – Adverse event definitions used in the trial (adapted from INTERMACS)

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<td><strong>Peri-Operative Myocardial Infarction</strong></td>
<td>The clinical suspicion of myocardial infarction together with CK-MB or Troponin &gt; 10 times the local hospital upper limits of normal, found within 7 days following VAD implant together with ECG findings consistent with acute myocardial infarction. (This definition uses the higher suggested limit for serum markers due to apical coring at the time of VAD placement, and does not use wall motion changes because the apical sewing ring inherently creates new wall motion abnormalities.)</td>
</tr>
</tbody>
</table>
| **Non-Perioperative Myocardial Infarction** | The presence at > 7 days post-implant of two of the following three criteria:  
   a) Chest pain which is characteristic of myocardial ischemia,  
   b) ECG with a pattern or changes consistent with a myocardial infarction,  
   c) Troponin or CK (measured by standard clinical pathology/laboratory medicine methods) greater than the normal range for the local hospital with positive MB fraction (≥ 3% total CK). This should be accompanied by a new regional LV or RV wall motion abnormality on a myocardial imaging study. |
| **Neurological Dysfunction** | Any new, temporary or permanent, focal or global neurological deficit ascertained by a standard neurological examination (administered by a neurologist and documented with appropriate diagnostic tests and consultation note). The examining physician will distinguish between a transient ischemic attack (TIA), which is fully reversible within 24 hours (and without evidence of infarction), and a stroke, which lasts longer than 24 hours (or less than 24 hours if there is evidence of infarction). The neuromotor assessment must be re-administered at 30 and 60 days following the event to document the presence and severity of neurological deficits. Each neurological event must be subcategorized as:  
   1) Transient Ischemic Attack (acute event that resolves completely within 24 hours with no evidence of infarction)  
   2) Ischemic or Hemorrhagic Cerebrovascular Accident/CVA (event that persists beyond 24 hours or less than 24 hours associated with infarction on an imaging study).  
   In addition, to above, for subjects < 6 months of age, any of the following:  
   3) New abnormality of head ultrasound  
   4) EEG positive for seizure activity with or without clinical seizure |
| **Psychiatric Episode** | Disturbance in thinking, emotion or behavior that causes substantial impairment in functioning or marked subjective distress requiring intervention. Intervention is the addition of new psychiatric medication, hospitalization, or referral to a mental health professional for treatment. Suicide is included in this definition. |
| **Renal Dysfunction** | Two categories of renal dysfunction will be identified:  
   **Acute Renal Dysfunction** Abnormal kidney function requiring dialysis (including hemofiltration) in subjects who did not require this procedure prior to implant, or a rise in serum creatinine of... |
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<tr>
<td>Respiratory Failure</td>
<td>Impairment of respiratory function requiring reintubation, tracheostomy or (for subjects older than age 5 years) the inability to discontinue ventilatory support within six days (144 hours) post-VAD implant. This excludes intubation for re-operation or temporary intubation for diagnostic or therapeutic procedures.</td>
</tr>
<tr>
<td>Right Heart Failure</td>
<td>Symptoms and signs of persistent right ventricular dysfunction [central venous pressure (CVP) &gt; 18 mmHg with a cardiac index &lt;2.0 L/min/m² in the absence of elevated left atrial/pulmonary capillary wedge pressure (greater than 18 mmHg), tamponade, ventricular arrhythmias or pneumothorax] requiring either RVAD implantation or inotropic therapy; or requiring inhaled nitric oxide or inotropic therapy for a duration of more than 1 week at any time after LVAD implantation.</td>
</tr>
<tr>
<td>Arterial Non-CNS Thromboembolism</td>
<td>An acute systemic arterial perfusion deficit in any non-cerebrovascular organ system due to thromboembolism confirmed by one or more of the following:</td>
</tr>
<tr>
<td></td>
<td>1) Standard clinical and laboratory testing</td>
</tr>
<tr>
<td></td>
<td>2) Operative findings</td>
</tr>
<tr>
<td></td>
<td>3) Autopsy findings</td>
</tr>
<tr>
<td></td>
<td>This definition excludes neurological events.</td>
</tr>
<tr>
<td>Venous Thromboembolism Event</td>
<td>Evidence of venous thromboembolic event (e.g. deep vein thrombosis, pulmonary embolism) by standard clinical and laboratory testing.</td>
</tr>
<tr>
<td>Wound Dehiscence</td>
<td>Disruption of the apposed surfaces of a surgical incision, excluding infectious etiology, and requiring surgical repair.</td>
</tr>
<tr>
<td>Other</td>
<td>An event that causes clinically relevant changes in the subject’s health (e.g. cancer).</td>
</tr>
</tbody>
</table>
SUPPLEMENTAL FIGURE 1: Death while supported on EXCOR.

A. Early peaking (blue) and late rising (red) hazard phases resolved from EXCOR mortality data.
**SUPPLEMENTAL FIGURE 1:** Death while supported on EXCOR.

**B.** Overall instantaneous risk of death (hazard function), as sum of hazard phase components. Dashed lines represent a confidence band around hazard estimates equivalent to one standard error.
SUPPLEMENTAL FIGURE 1: Death while supported on EXCOR.

C. Survival curve, enclosed by a confidence band equivalent to one standard error. Superimposed are non-parametric Kaplan-Meier estimates with a circle at each death and confidence bars also equivalent to one standard error. Number of patients remaining at risk is shown below figure.
SUPPLEMENTAL FIGURE 2: Relationship of survival on EXCOR® support to patient weight at implant. This is a nomogram of multivariable equation in Table 3 using the following assumptions: LVAD implant, GFR normal at implant, serum bilirubin = 1.0 mg/dL.
SUPPLEMENTAL FIGURE 3: Relationship of survival on device to bilirubin. This is a nomogram of multivariable equation in Table 3 using the following assumptions: Patient weight=10kg, LVAD implant, Normal GFR for age.