Overcoming the Size Barriers in Pediatric Ventricular Assist Device Support

By

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ABSTRACT

Mechanical circulatory support has become a therapeutic option for children with advanced heart failure. This type of support is often used to bridge patients to heart transplantation with approximately a third of all patients listed for transplant requiring some form of mechanical support. While there are a number of different devices to choose from the outcomes for the different devices may vary based on patient characteristics including size. Therefore a research program was established to address the following questions to help guide the management of pediatric patients with advanced heart failure:

1.What are the clinical characteristics of children <10Kg undergoing mechanical circulatory support (MCS) as a bridge to transplant?

2.How do infants <10Kg with cardiomyopathy (CM) vs. congenital heart disease (CHD) requiring MCS pre-transplant differ?

3.What are the outcomes for children <10Kg based on the first MCS device used as a bridge to transplant (ECMO vs.VAD)?

4.What are the clinical characteristics of pediatric patients receiving a Heartware HVAD System?

5.What are the outcomes of pediatric patients receiving a Heartware HVAD System?

6.Does the survival for children with a Heartware HVAD system differ based on body surface area (BSA ≤ 1m2 vs. >1m2)?

PREFACE

This thesis is an original work by Jennifer Conway. Chapter 2 was done in conjunction with the Pediatric Heart Transplant Society (PHTS) after a competitive call for proposals, where this project was picked by the PHTS scientific committee after peer review as one of the top three proposals. The Pediatric Heart Transplant Society has the largest and most comprehensive registry on patients who are listed for and undergo heart transplantation. There are currently over 9000 patients in the database listed for transplant and over 7000 who have undergone transplantation (https://www.uab.edu/medicine/phts/). The design of the research project, literature review, and the statistical design were done by the main author, Jennifer Conway. The statistical analysis was done in conjunction with the statisticians at the data coordinating center at the University of Alabama, where PHTS resides. The entire manuscript was written and prepared by Jennifer Conway and edited accordingly after feedback from the co-authors and journal reviewers. Chapter 2 has been accepted by the Journal of American Heart Association, and permission has been obtained to use the manuscript as part of this thesis.

Jennifer Conway, Ryan Cantor, Devin Koehl, Robert Spice, Dipankar Gupta, Michael McCulloch, Alfred Asante-Korang, Dean. T. Eurich, James K. Kirklin, Elfriede Pahl. Survival after Heart Transplant Listing for Infants on Mechanical Circulatory Support. Journal of American Heart Association, 2020: 9(11).

The research project for Chapter 3 received ethics approval from the University of Alberta Ethics Board (Worldwide Experience with Heartware HVAD Implants, Pro000555910, March 23, 2015). Chapter 3 was designed, executed and data collected by the author, Jennifer Conway. Data analysis was done in conjunction with Chu-Po S Fan from the Cardiovascular Data Management center at The Hospital for Sick Children in Toronto, Ont. Jennifer Conway wrote the manuscript and revised it based on feedback from co-authors and the reviewers from the journal. Chapter 3 has been published, and permission has been obtained to utilize the manuscript as part of the thesis:

Jennifer Conway, Oliver Miera, Iki Adachi, Katsuhide Maeda, Pirooz Eghtesady, Heather T Henderson 6, Kristine Guleserian, Chu-Po S Fan, Richard Kirk, Pediatric VAD Investigators. Worldwide Experience of a Durable Centrifugal Flow Pump in Pediatric Patients. Semin Thorac Cardiovasc Surg. 2018: 30(3):327-335.

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The author wishes to acknowledge the Pediatric Heart Transplant Society for their support and assistance. Without them, the completion of this thesis would not have been possible. In addition, I would like to acknowledge the global pediatric VAD community for their willingness to collaborate and share their center experiences. Without this type of collaboration, it would be impossible to understand the outcomes of children with VAD therapy, given the numbers at each pediatric center are small.

The author would also like to acknowledge all my coauthors on the two manuscripts who provided valuable feedback and encouragement. I would specifically like to mention Dr. Elfriede Pahl, who has been a great mentor and provided ongoing encouragement and motivation during this process.

The author would also like to thank Dr. Andrew Mackie for taking the time to be part of my committee and finding opportunities for me to continue to advance my career. Lastly, I would like to thank Dr. Dean Eurich for his patience and support. His guidance helped me navigate this process and allowed me to find a balance between my full-time job and the academic demands of the Masters of Science Program.

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List of Abbreviations

ACC: American College of Cardiology

AHA: American Heart Association

AVVR: Atrioventricular Valve Regurgitation

BIVAD: Biventricular Assist Device

BSA: Body Surface Area

BTT: Bridge to Transplant

CI: Confidence Interval

CM: Cardiomyopathy

CHD: Congenital Heart Disease

COC: Competing Outcome Curve

ECMO: Extracorporeal Membrane Oxygenation

IQR: Interquartile Range

LVAD: Left Ventricular Assist Device

MCS: Mechanical Circulatory Support

HCM: Hypertrophic Cardiomyopathy

HF: Heart Failure

HR: Hazard Ratio

HTx: Heart Transplant

Kg: Kilogram

UNOS: United Network for Organ Sharing

PHTS: Pediatric Heart Transplant Society

RVAD: Right Ventricular Assist Device

1 INTRODUCTION

1.1 Heart Failure in Children

Heart failure is generally defined as the heart's inability to pump enough blood to meet the demands of the tissues and organs. In the pediatric population, as defined by an age ≤ 18 years of age, heart failure can occur for a variety of reasons and present at any time from in-utero until 18 years of age. Heart failure can develop in the context of uncorrected congenital heart disease or in those patients with end-stage congenital heart disease. In addition, heart failure can arise from cardiomyopathies (weak heart muscle) or acquired diseases like myocarditis (infection of the heart). Table 1 outlines some of the conditions in pediatrics that can result in heart failure. However, regardless of the cause, the features and presentation are similar.

The presentation of heart failure varies but consists of a constellation of symptoms including increased work of breathing, edema, poor exercise tolerance, poor growth and gastrointestinal symptoms, making the diagnosis difficult due to similarities with other pediatric conditions (1). There are several classification systems to describe the degree of symptoms a patient with heart failure is experiencing. In adult patients, the New York Heart Association Classification (Table 2) is used to describe a patient's symptoms and is based on the increasing severity of symptoms (2). While this can be utilized in adolescents, it is less useful for younger children or infants. For younger patients, the ROSS classification system could be used. However, it has never been validated, and the prognostic value is unknown, making it not widely used in pediatrics (See Table 3) (3). A useful classification system is the American College of Cardiology (ACC)/American Heart Association (AHA) Stages of Heart Failure (Table 4) (4). This tool is based on the development and progression of disease and has been used to suggest treatment strategies in adults (4).

Symptom presentation can also be classified into four main groups and utilized to help guide medical management. These groups are based on perfusion (a marker of how much blood the tissues are seeing) and the degree of congestion (a marker of how much extra fluid the patient has retained) (Figure 1) [3]. Patients with Class A and B symptoms can be managed with oral and occasionally intravenous (IV) medications such as angiotensin converting enzyme inhibitors, beta-blockers and diuretics (Figure 2). Patients with Class C or D symptoms can be managed with intravenous diuretics, inotropes, mechanical ventilation and in some mechanical circulatory support (MCS), such as extracorporeal membrane oxygenation (ECMO) or a ventricular assist device (VAD).

While it is unknown what proportion of children in heart failure have Class C or D symptoms, there has been a recent increase in heart failure admissions in patients in the United States, with a third of these patients dying or requiring heart transplantation within the same hospitalization (5). This is also supported by data from the International Pediatric Heart Failure registry that found that most pediatric patients who present in heart failure for the first time require hospital admission (84%). Moreover, most of those patients were managed in an intensive care unit due to the severity of their illness, with 16% requiring a VAD and 28% a heart transplant with their first presentation (6).

A recent systemic review has been published that has attempted to bridge the knowledge gap about the burden of this condition in paediatrics including: hospitalization, cost, need for transplant and mechanical support (7). This review identified 18 studies focused on heart failure in children <18 years of age regardless of the etiology over a 10-year period and showed infants <1 year of age had a higher rate of heart failure related admissions compared to older children. In addition, the treatment of heart failure in infants resulted in a longer length of stay and a more costly course. Mortality in children with heart failure varied across studies but was shown to increase with the severity of heart failure from 7.4% for confirmed heart failure to 71% in those with heart failure who have a cardiac arrest.

Patients with end stage heart failure or heart failure refractory to medical management, such as those described above, are patients that would be assessed for a heart transplant to determine if they were eligible. However, given the high percentage of deaths on the transplant waitlist, advanced forms of therapy, such as MCS are required to bridge patients to transplant to improve survival, reverse any damage to organs and allow for ongoing rehabilitation prior to transplant.

1.2 Prevalence and Incidence of Heart Failure

Information on the prevalence and incidence of heart failure in pediatric patients has been very limited, with many regional variations due to varying etiologies. A recent systematic review identified five studies that reported the incidence of heart failure. The incidence of new-onset heart failure in the United Kingdom and Ireland was 0.87 per 100 000 population, with a range from 0.11-1.27 per 100 000 depending on the region (8)(9). With respect to hospitalizations due to heart failure, the review identified two German studies that reported an incidence of 2-3 hospitalizations per 100 000 population. This number was much higher in Taiwan, with an incidence of 7.4 hospitalizations per 100 000 population. The prevalence was also examined in the systematic review with one study from Spain, suggesting a prevalence between 0.1-0.6% of pediatric patients depending on the population examined (9). In the cardiomyopathy/myocarditis patient population, which is one of the common group of patients that that undergo MCS therapy and heart transplantation, the prevalence of heart failure varies based on the etiology of the cardiomyopathy. However, the majority of patients with dilated cardiomyopathy present in heart failure, with restrictive cardiomyopathy being the next most common cardiomyopathy to present in heart failure (9).

There is currently minimal data on the incidence or prevalence of heart failure or heart failure hospitalization in pediatric patients in Canada(10). A recent analysis of 4,693 heart failure hospitalizations in 3,523 children in Canada showed that the annual number of heart failure hospitalizations ranged from 7 to 10 per 100,000 children per year. While this number is higher than previous reports, it included patients with unrepaired congenital heart lesions, many of which can be treated effectively with corrective surgery and therefore do not accurately represent the patient population that will be addressed in this report.

While it is unclear how many children will present with end stage heart failure requiring a ventricular assist device, what is known is that in patients listed for a heart transplant, approximately 30% require some form of MCS with a VAD being the most common (11). Mechanical support is more common in children with a dilated cardiomyopathy compared to those with a congenital heart lesion, with over 50% of children over the age of six with a dilated cardiomyopathy requiring MCS as a bridge to transplant (11). The decision regarding the most appropriate type of MCS or even VAD is complex and is currently based on the patient's size and etiology of the heart failure.

1.3 Current Management

The management of heart failure is dependant upon the clinical condition of the patient at presentation. For children with mild heart failure, they can often be managed with oral heart failure medications in an outpatient setting (1). For children with moderate heart failure, they may require admission to the hospital to optimize oral medications or the initiation of intravenous medications (1). Children with severe heart failure will often be managed in an intensive care setting with intravenous inotropes, intravenous diuretics, ventilation if required, sedation, and nutrition support. If these children develop signs of end-organ injury, a second organ system failure or the need for two intravenous inotropes, than a discussion about MCS usually occurs, and these children would be assessed for a heart transplant. In a non-acute setting, a ventricular assist device is generally preferred over extracorporeal membrane oxygenation (ECMO) as a way to bridge children to transplant due to the better outcomes and morbidity profile of VADs over ECMO. However, it is unclear if this finding is universal across all size groups (12). VAD therapy in Pediatrics began in the 1990s in Berlin, Germany, with the invention of the Berlin Heart EXCOR Device (Figure 1.3). This device is a paracorporeal pulsatile device that requires a child to remain in hospital until transplant. It is the only device approved by the Federal Drug Administration (FDA) in the United States for use in children. For many years this was the primary device available for children until the introduction of the Heartware HVAD system (Figure 1.4). The Heartware HVAD system has never been approved for use in children, but implants in children began in 2010 due to the smaller size of the device compared to previous adult devices. The Heartware HVAD is a continuous flow pump that is fully implantable, except for a driveline that connects to a controller and battery. Due to its design, it expanded VAD therapy for children by opening up the opportunity for children and adolescents to be discharged home.

Outcomes of VAD therapy have been tracked through a number of different registries. The Pedimacs Registry is a North American registry that began tracking children's outcomes on VAD support in 2012. A recent report confirms that the most common reason for VAD implantation is dilated cardiomyopathy, followed by congenital heart disease. Patients implanted with a pulsatile device (ex: Berlin Heart EXCOR) now tend to be younger (mean age 3.3 yrs ± 3.9 years), sicker (77% intubated) and with a higher proportion of patients with CHD (21%) compared to the cohort of patients with an intracorporeal continuous-flow device (ex: Heartware device) (mean age 14.3 +/- 3,8 years; 21% intubated and 12% CHD)(13). In addition, a previous study showed that children <10 Kg who are supported on a pulsatile device achieved a successful outcome only 57% of the time, with the diagnosis of congenital heart disease and liver dysfunction being a significant risk factor for death while awaiting heart transplant (14). In addition, within the group of patients who are <10 Kg, the subgroup of those <5 Kg were at higher risk for morbidity and mortality(12,14–17).

The patients supported on pulsatile devices and intracorporeal continuous flow devices form the largest bulk of children on VAD support in pediatrics and given their size differences and difference in VAD strategy face different challenges that will be explored in this thesis.

1.4 Research Objectives

Given the limited knowledge to guide front-line clinicians concerning the approach to management of the youngest children with traditional devices and older children with newer adult devices, a research program was established to address the current evidence gaps. Specifically, the objectives were:

1. Describe the clinical characteristics of children <10Kg undergoing mechanical circulatory support (MCS) as a bridge to transplant.
2. Compare the outcomes of infants <10Kg with cardiomyopathy (CM) vs. congenital heart disease (CHD) requiring MCS pre-transplant
3. Compare the outcomes for children <10Kg based on the first MCS device used as a bridge to transplant (ECMO vs.VAD)
4. Describe the cohort of pediatric patients receiving a Heartware HVAD System
5. Described the outcomes of pediatric patients receiving a Heartware HVAD system
6. Compare the survival outcomes for children with a Heartware HVAD system based on body surface area (BSA ≤ $1m^2$ vs. >$1m^2$)

1.5 Organization of Research

This thesis follows a paper-based format, containing two different manuscripts. Chapter 1 provides background information on pediatric heart failure and ventricular assist devices. The second chapter addresses the ongoing controversy about the best way to support children to transplant with MCS who are <10Kg and in particular, those with congenital heart disease. Although most studies have suggested that VAD therapy is superior to ECMO support in pediatric patients to bridge to transplant, this has not

been elucidated in the cohort of patients <10Kg. Therefore, by utilizing the data available in the Pediatric Heart Transplant Society Registry, outcomes of infants <10Kg with cardiomyopathy (CM) vs. congenital heart disease (CHD) were compared based on the choice of mechanical circulatory support (ECMO vs. VAD) that was implanted pre-heart transplant.

The third chapter represents the first and only international pediatric VAD study in the literature. At the time of the design, there was limited information available to help practitioners understand the outcomes of the Heartware HVAD system in children (18–24). In addition, it was not clear what the lower weight limit was for implantation or the outcomes in children that had a BSA less than the recommended size for implant. Moreover, as all previous VAD patients had stayed in the hospital, this study explored whether discharge was a possibility in the pediatric population.

Lastly, Chapter 4 provides a general discussion of study results, limitations and implications for clinicians as well as future research directions.

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1.7 Tables

Table 1.1: Etiology of Heart Failure in Children

	Examples
Acquired Heart Disease	Infection Post Chemotherapy Drugs/Toxins Nutritional Deficiencies
Congenital Heart Disease	Uncorrected heart defects Failed surgical palliation
Genetics or Metabolic Conditions	Muscular Dystrophies Mitochondrial Disorders
Cardiomyopathies	Dilated Restrictive Hypertrophic Ischemic

Table 1.2: New York Heart Association Classification

Class I	No symptoms during ordinary activity
Class II	Mild symptoms during activity with some limitation
Class III	Marked limitation in exercise capacity with symptoms on mild exertion
Class IV	Symptoms at rest

Table 1.3: Ross Classification

Class I	No limitations or symptoms
Class II	Mild tachypnea or diaphoresis with feeding in infants Dyspnea on exertion in older children No growth failure
Class III	Marked tachypnea or diaphoresis with feeds or exertion Prolonged feeding times Growth failure from heart failure
Class IV	Symptoms at rest with tachypnea, retractions, grunting or diaphoresis

Table 1.4: AHA/ACC Classification of Heart Failure

Stage	Description	Examples
A	• Patients at high risk of developing HF • No identified structural or functional abnormalities • Never had signs or symptoms of HF	• Family history of CM • History of cardiotoxic drug therapy • Systemic condition
B	• Structural heart disease • Never had signs or symptoms of HF	• Ventricular hypertrophy, fibrosis or dilation • AVVR
C	• Underlying structural heart disease • HF symptoms- past or present	• HF patients on treatment • Dyspnea or fatigue due to LV systolic dysfunction
D	• Advanced structural heart disease • HF symptoms at rest despite maximal medical therapy • Require specialized interventions	• Patients in hospital awaiting cardiac transplantation • Home inotropes • MCS • Frequent hospitalization for HF

1.8 Figures

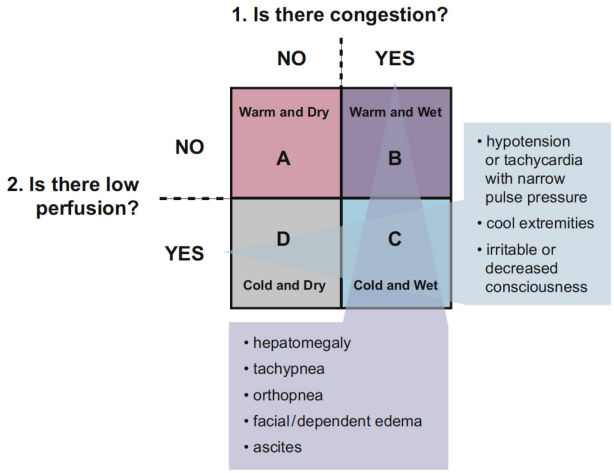

Figure 1.1: Clinical presentation of pediatric heart failure based on symptoms of congestion and perfusion

(1)

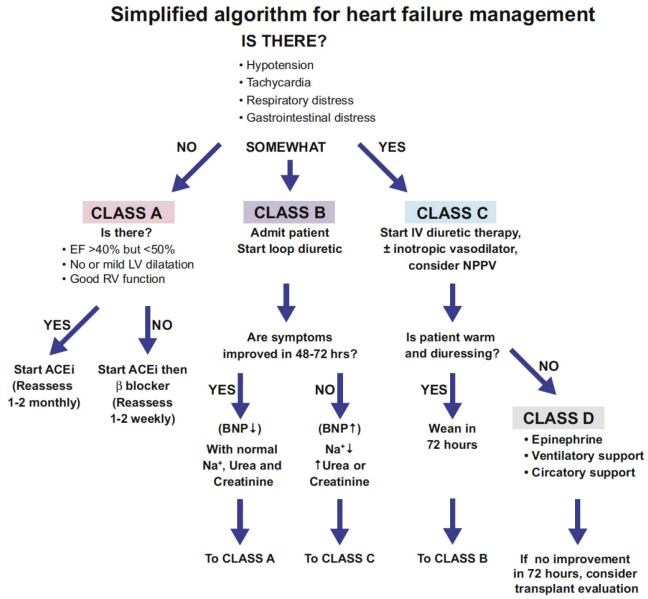

Figure 1.2: Class A through D heart failure symptoms and suggested management

(1)

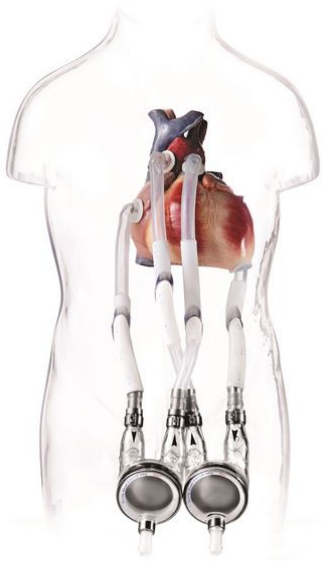

Figure 1.3: Schematic representation of the Berlin Heart EXCOR with support of the left and right side of the heart

(https://www.berlinheart.com/medical-professionals/excorr-pediatric/)

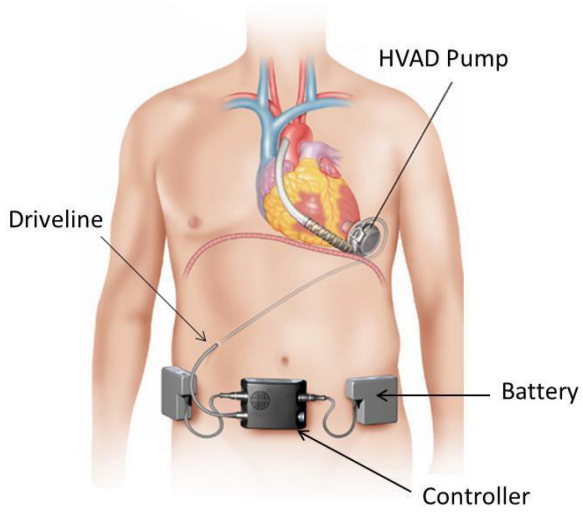

Figure 1.4: Schematic of the Heartware HVAD system

(http://www.heartware.com/sites/default/files/uploads/resources/ifu00184_rev07_patientmanual_uspma.pdf)

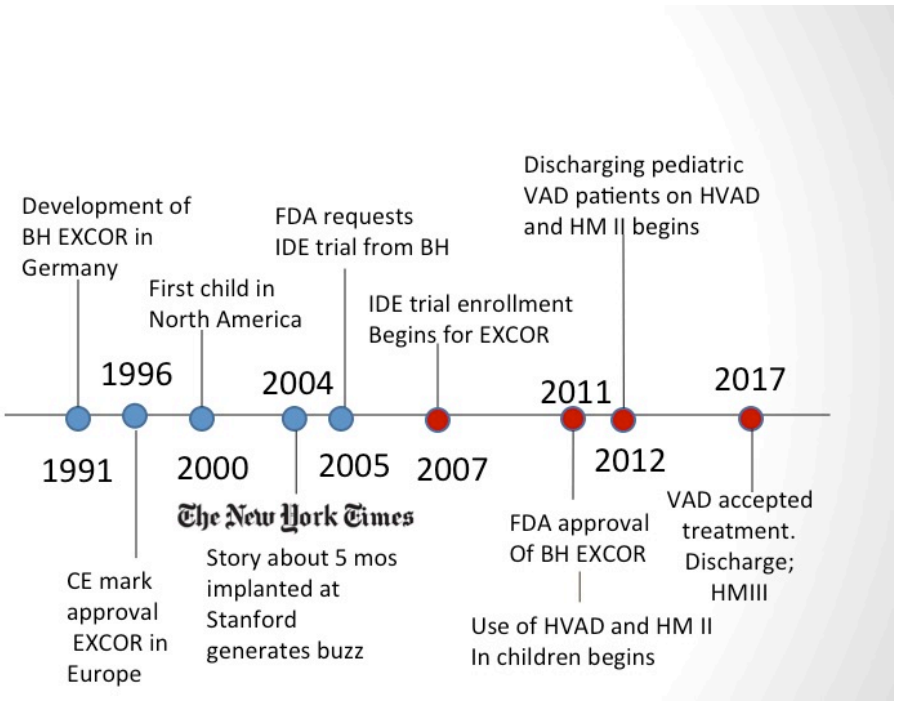

Figure 1.5: Timeline of pediatric VAD therapy

2 CHAPTER 2: SURVIVAL AFTER HEART TRANSPLANT LISTING FOR INFANTS ON MECHANICAL CIRCULATORY SUPPORT

Jennifer Conway, Ryan Cantor, Devin Koehl, Robert Spicer, Dipankar Gupta, Michael McCulloch, Alfred Asante-Korang, Dean. T. Eurich, James K. Kirklin, Elfriede Pahl. Survival after Heart Transplant Listing for Infants on Mechanical Circulatory Support (Accepted Journal of American Heart Association)

2.1 Introduction

Mechanical circulatory support (MCS) is an important component in the management of end stage heart failure in children (1-4). While extracorporeal membrane oxygenator (ECMO) support has historically been the predominant form of support, advancements in the field of ventricular assist devices (VAD) have resulted in a transition away from ECMO as first line therapy.

This transition away from ECMO has likely been driven by the increase in availability and experience with VADs; however, the choice of device is dependent on the patient's size, anatomy, and clinical condition; with options being more limited in smaller patients as well as those with congenital heart disease (CHD). For children who require longer-term support as a bridge to transplant (BTT), primary implantation of a durable device has become the preferred modality of support, over ECMO, with the possible exception of those with profound cardiogenic shock with multi-organ dysfunction. This shift in clinical practice is based on a number of studies examining the outcomes of children undergoing BTT with MCS (1-2)

However, it is unclear if survival with various forms of MCS is significantly different for infants requiring MCS as BTT, especially in the subset of patients who are small and those with CHD. Previous studies have shown that children <10 Kg who are supported on a durable device achieved a successful outcome 57% of the time; however, CHD and liver dysfunction significantly increased the risk of death while awaiting HTx (5). In addition, it has been suggested that within the group of patients who are <10 Kg, the subgroup of those <5 Kg are at higher risk for morbidity and mortality (1-5)

Currently, no studies have compared survival between ECMO and other forms of device therapy available for the smallest children (<10 Kg). Based on data from a recent analysis of the United Network for Organ Sharing (UNOS) database, the frequency of VAD therapy as a BTT in infants <10Kg is similar to that of ECMO (10.3% vs. 9.3%) (6). This observation differs from the trends seen in older children (6,7). It is unclear if this practice variation is driven by outcomes. Therefore, further information is needed on the outcomes of device therapy in this unique and complex patient population. We sought to compare the outcomes of infants <10Kg with cardiomyopathy (CM) vs. congenital heart disease (CHD) requiring MCS pre-HTX.

2.2 Methods

2.2.1 Patient Selection and Data Collection

The Pediatric Heart Transplant Society (PHTS) maintains a multicenter prospective event driven database that enrolls patients who are younger than 18 years of age that have been listed for HTx. Data for this study was obtained from the PHTS database from January 1, 2010, to December 30, 2018, and included all patients from 55 participating institutions (Supplemental Information 2.1).

Institutional Review Board approval was obtained at each institution. The Data Collection and Analysis Center is located at the University of Alabama at Birmingham. Information is collected on demographics and event data surrounding listing, transplantation, and death. Clinical information for any listing in PHTS is reported on the date of listing. The indications for listing and the decision for MCS and HTx were made at the discretion of the primary medical team on the basis of individual institutional clinical practice.

2.2.2 Study Cohort and Comparison Groups

The study included all children with weight <10 kg at the time of listing who were diagnosed with CHD or cardiomyopathy (CM)/myocarditis (Figure 2.1). For CHD patients, multiple secondary diagnosis details are collected. A small number of patients were excluded from the analysis due to having a different primary diagnosis (n=15).

Patient characteristics were compared by diagnosis group and by the presence and timing of initial MCS support. Patients were either supported by ECMO or VAD at the time of listing or were unsupported at the time of listing. Additionally, the patients that were unsupported at the time of listing could have received MCS after listing.

Both temporary and durable devices were included in the study. The term temporary device was used for devices that traditionally have been used for short-term support, including: Abbott PediMag™ and CentriMag™, Maquet Rotaflow, Sorin Revolution, TandemHeart. This definition was solely based on device type and not the duration of support. All other devices were considered durable devices.

2.2.3 Statistical Analysis

Differences in demographic and clinical characteristics between the groups were determined by independent t-tests for continuous variables and reported as means ± standard deviation or median and IQR. For categorical variables, chi-square testing was performed and reported as frequency and percentage.

To accurately compare the risk of death on the waitlist after MCS initiation (ECMO or VAD), patient time was segmented as prior to MCS initiation or without MCS initiation or after MCS initiation. For patients on support at listing, the start time of MCS was the day of listing, and their entire follow-up was categorized

based on support at listing. For patients unsupported at listing and initiating MCS after listing, follow-up time was segmented to prior to MCS initiation (with censoring at the initiation of MCS) and then transition to after MCS based on the implant date until reaching a registry endpoint. This patient level outcome after VAD initiation was selected because most patients received no or only one device. This same approach was also used for patients with ECMO. Using this patient time segmentation approach, Kaplan-Meier analysis was used to evaluate survival on the waitlist and compare survival without MCS to survival after MCS initiation with either ECMO or VAD. Additional comparisons were made for patients based on etiology and size. Survival on the waitlist after ECMO as a bridge to VAD was compared to survival on the waitlist after initiating MCS directly with VAD and to survival on the waitlist after ECMO support prior to or without a bridge to VAD.

Multiphase parametric hazard modelling (8) was used to evaluate the risk of death on the waitlist in the following patient groups: 1) ECMO patients, 2) VAD, 3) CHD patients, 4) CM /Myocarditis patients. Patient time was segmented by support initiation, as described above. Numerous factors were evaluated as covariates (Supplemental Information 2.2). Final models were determined using forward stepwise selection with an entry alpha of 0.1 and an exit alpha of 0.05. The final models were used to depict predicted mortality curves for different patient scenarios.

Competing outcome analysis was used to evaluate the time related probabilities of the mutually exclusive device related outcomes for MCS initiation with VAD (HTx from VAD, death on VAD, switch to ECMO, explant) and for MCS initiation with ECMO (HTx from ECMO, death on ECMO (death on ECMO or within one week of decannulation), switch to VAD, decannulation). In the competing outcome depictions, at any given point in time, the sum of the percentages for each mutually exclusive event equals 100%. The statistical analysis was performed using SAS package 9.4, Cary, NC.

2.3 Results

2.3.1 Demographics and Clinical Characteristics of all Infants

Between 2010-18, 4728 patients were listed for primary HTx in PHTS, of which the study group consisted of the 2049 patients having a weight of <10 Kg at the time of listing. Within the study group, 40.2% (n=823) had a diagnosis of CM and 59.8% (n=1226) had CHD. In terms of MCS, 269 (13.1%) (n=110 CM and n=159 CHD) required ECMO support and 308 (15%) (n=222 CM and n= 86 CHD) required VAD support at or after listing. There were 1472 patients that remained, which did not require MCS support during their entire time on the waitlist (Figure 1).

Table 1 highlights the demographic characteristics and differences between the CHD and CM cohorts. Notably, the CHD patients were younger, smaller and less likely to be on inotropes at listing. These patients also had a tendency towards a higher listing creatinine but similar levels of total bilirubin as CM patients.

2.3.2 Use of Mechanical Support of All Infants <10Kg

Figure 2.1 outlines the patients supported with MCS, including the timing of first MCS support. For those listed on MCS, time in days on ECMO prior to listing was a median of 4d (2-7) and for VAD 5d (1, 13). For those not on device therapy at listing, but who eventually required MCS initiation, the time from listing to ECMO initiation was a median of 20.5 days (9, 47), and VAD was a median of 13 days (5, 35). The demographics varied across device strategy at listing with a higher proportion of children <5 Kg undergoing ECMO support at the time of listing. In addition, as outlined in Table 2.2, the weights, ages, previous history of surgery, bilirubin and creatinine differed across the support strategies at listing. For all infants on VAD therapy, the majority underwent isolated Left VAD (LVAD) implantation (n=238, 77.3%), 37 patients (17.7 %) required biventricular VAD (BiVAD) support, and 14 received an isolated Right VAD RVAD) (4.5%).

When further examined, only 9.5% (n=117) of patients with CHD were on some form of MCS at listing (VAD n=29 and ECMO n=88), compared to 139 (16.9%) patients with CM (VAD n=66 and ECMO n=73) ($p<0.001$). Following listing, an additional 57 CHD patients underwent VAD implant, and 71 were placed on ECMO, as compared to 156 unique CM patients who underwent VAD implant and 37 ECMO after listing (Figure 2.1). Among CHD patients receiving MCS, the median time between listing and MCS was 0.6 months (0.3-1.3) and was similar to those with CM, [0.59 months (0.25-1.3)].

2.3.3 MCS in Infants with Congenital Heart Disease

The majority of patients in the CHD cohort were male (n=701, 57.2%), with 75.9% having a previous history of cardiac surgery prior to listing (Table 2.1). Within this patient group, there were differences in the weight and age distribution of CHD patients based on initial MCS strategy at listing, with those on ECMO at listing being younger and smaller than those who underwent VAD placement or who did not require MCS at listing (Table 2.3). History of prior cardiac surgery differed between the three groups, as the majority of infants in the ECMO group at listing underwent previous heart surgical interventions. There were significantly more infants with single ventricles in the ECMO and unsupported groups, compared to single ventricle patients on VAD support. Also, end-organ function differed at listing between the three groups with the total median bilirubin level in the ECMO and unsupported cohort being higher than the VAD group. There was a higher percentage of patients in the ECMO group that had a history of renal insufficiency, but at the time listing, there was no difference in the mean creatinine level. The diagnosis for all patients with CHD <10 kg included in this cohort is outlined in Table 2.5.

The listing characteristics of CHD patients with MCS at listing compared to initiation after listing are also outlined in Table 2.3. Those patients who were on support at listing were more likely to be ventilated, have a history of previous cardiac surgery and history of renal insufficiency and a slightly higher creatinine at the time listing compared with those patients where MCS was initiated after listing.

2.3.4 MCS in Infants with CM

The majority of patients with CM were female, with over 70% on inotropes and 40% requiring a ventilator at listing (Table 2.1). In general, the weight and age of the CM patients at listing were higher than those with CHD. Within the CM group, those patients with ECMO at listing (Table 2.4) were more likely to be ventilated, have a history of renal insufficiency, higher bilirubin and creatinine at listing and were smaller than those on VAD or unsupported. CM patients on MCS at listing had a higher proportion of patients on ventilators with a history of renal insufficiency compared to those where MCS was initiated after listing. In addition, the average listing bilirubin and creatinine were higher (Table 2.4).

2.3.5 Survival for all Patients <10 Kg

In the overall group (CM + CHD), waitlist survival was significantly different between those who required ECMO or VAD support at any time, compared to those that did not (Figure 2.2). Furthermore, comparison of survival estimates at the 3-month time point (3 months after device placement for those who required ECMO or VAD) demonstrates a better survival for VAD compared to patients supported with ECMO (74.3 % vs. 48.6%, $p<0.0001$) (Figure 2.2). This survival advantage was also observed for patients that were able to transition from ECMO to VAD (Figure 2.3). This difference in outcomes between ECMO and VAD was observed in both the CHD and CM populations, with a greater negative impact on the CHD cohort (Figure 2.4). By three months post implant, the survival after support in the CM group was 62.2% with ECMO compared to 81.2% on VAD support (Figure 2.4). For the CHD group, however, survival dropped to 38.9% for the ECMO group vs. 57.7% for the VAD support cohort at three months.

As mentioned above, within the CHD population requiring MCS, outcomes after device placement while waiting for HTx are not equivalent between MCS types. However, they were not statistically different in outcomes between single ventricle and biventricular hearts (Figure 2.8: Supplemental Figure). There was a significant survival advantage to support with VAD as compared to ECMO with the CHD population, and this was also demonstrated when patients with both CM and CHD were able to transition from ECMO to VAD support during the waiting period (Figure 2.5A, 2.5B).

2.3.6 Competing Outcomes

The competing outcomes curves for VADs in children with CHD show that at 1-month post implant, 67.2% were alive on VAD therapy, 15.2% were transplanted, 5.8% had died, and 5.9% had been switched to ECMO and 5.8% were explanted (Figure 2.6A). Curves for ECMO therapy in CHD patients at 30 days, 10.7% were alive on ECMO, 35.2% of the patients had died, 27.7% had been decannulated, 13.2% were switched to a VAD and 13.2% had undergone HTx (Figure 2.6C).

When examining device related outcomes in the CM patients at 1-month post VAD implant, 60.0% were alive on VAD therapy, 17.8% were transplanted, 6.4% had died, and 2.3% had been switched to ECMO and 13.7% explanted (Figure 2.6B). For ECMO therapy in CM patients revealed that at 30 days, 4.6%

were alive on ECMO, 13.6% of the patients had died, 30.0% had been decannulated, 39.1% were switched to a VAD and 13.6% had undergone transplant (Figure 2.6D).

2.3.7 Risk Models

Multivariate analysis was performed both for survival after first ECMO or VAD implantation while listed (Appendix 2.B). The models all revealed a single early decreasing hazard for death. This analysis confirmed that CHD was a risk factor for death on MCS when in infants <10Kg. For ECMO, the hazard of death was in the early phase (HR 2.70 (1.75-4.16, p<0.0001). For VAD therapy, the hazard for death also occurred in the early phase [HR 2.19 (1.31-3.66, p=0.003)]. In addition to diagnosis, weight was also associated with mortality in the VAD model but not ECMO (HR 0.32 for each unit change in the log scale, 0.17-0.61, p=0.0006), with a higher weight being protective. For example, the hazard ratio for mortality of a 6 Kg child compared to a 5 Kg child is 0.81 (Table 2.6).

Besides MCS specific hazard models, models were created for CM and CHD patients (Table 2.6). For patients with CM, the use of ECMO (HR 3.48, 2.16-5.6, <0.0001) and VAD (HR 1.83 1.17-2.86, P= 0.008) or a ventilator at listing (HR 1.79, 1.2-2.68, p=0.005) was associated with mortality in the early phase of the model. For patients with CHD, there were a number of factors associated with early phase mortality in the MV analysis, including: white race, list year since 2010 and higher weight being protective, while ECMO, VAD, status 1A at listing and ventilator support at listing being associated with mortality. The impact of size and difference between the CM and CHD group on outcomes can clearly be seen in the Kaplan Meier survival analysis (Figure 2.7), especially early after implant. In the smallest of patients, those <5 kg, overall survival did not differ between ECMO vs. VAD (p=0.099) for the CHD group or the CM group (p=0.38). However, survival was better on both forms of support for those <5Kg with a diagnosis of CM (Figure 2.7).

2.4 Discussion

This study explored the characteristics and outcomes of infants <10Kg that required MCS while awaiting HTx with attention to the mode of support and diagnosis. This particular group was chosen due to previously reported inferior outcomes while supported on MCS in this subset of patients. (5,9-11) A previous analysis through the PHTS examined all patients, regardless of age, supported on ECMO and found that just over half of the patients with CHD listed and transplanted were on ECMO (10) and that smaller children had the highest risk of mortality. Our analysis adds further to this previous analysis by examining further detail in those smaller patients requiring MCS and highlights the difference in outcomes for patients with CM compared to CHD (12).

This analysis, like others, found that ECMO was associated with higher mortality in both CHD and CM patients, but the difference was more striking in those with CHD. In CHD patients, death on ECMO at one-month was 35%, with only 15% of patients achieving HTx. This differed from CHD patients treated with VAD support, where death on VAD at one month was 5.8%. Interestingly, a similar proportion of

CHD patients underwent HTx (15.8%) in the COC analysis. We were able to show in this study that the ECMO survival disadvantage was reversed in patients who were able to switch to VAD support in both the overall cohort and children with CHD. While the above results incorporated all patients <10Kg, the story for those <5Kg was less clear. Similar to the overall cohort, those <5Kg with CM had better outcomes compared to CHD patients on support. However, from the KM survival analysis, there was no significant survival difference between ECMO and VAD within each group. These findings highlight the importance of finding alternative treatment options in these very small children.

While ECMO has traditionally been used as a means of MCS, VAD therapy provides an alternative strategy of MCS for children awaiting HTx. Although the majority of pediatric patients supported with VADs have a favourable outcome, the combination of CHD and small size has been suggested to have a significant impact on survival in this patient cohort (5,9). Currently, VAD support is the predominant means of support in most children, however as highlighted in this study, ECMO continues to play an important role in young infants, with 33.1% of CM patients and 64.9% of patients with CHD utilizing ECMO as the first device. The predominance of ECMO use in children with CHD may be driven by the known challenges of supporting these patients with VAD, the predominance of children <5Kg in this group, the need for an oxygenator and the use of ECMO as a first line strategy following congenital surgery.

While there are many factors that could be responsible for these differences in MCS outcomes between patients with CM and CHD, the role of cardiac surgery cannot be dismissed. A recent paper by Morales et al. showed that survival outcomes for infants on a pulsatile VAD who had pre-implant congenital heart surgery plus ECMO during the same admission had poor outcomes, with only 8% survival. In contrast, patients who did not have congenital surgery plus ECMO had a 61% survival. The authors cautioned that if patients had undergone pre-implant surgery plus ECMO, VAD support might not provide a survival benefit. While we know the number of patients in our study that underwent previous congenital heart surgery, we do not know what proportion had surgery during the same admission as the VAD implantation. Nevertheless, due to the high percentage of children with CHD <10Kg, we suspect that using VAD as a rescue therapy following surgery may have played a significant role in our results (13).

Our findings showing a difference in outcomes between infants with CM and CHD are supported by previous literature, including a report by Conway et al., who examined the outcomes of 97 patients <10Kg supported with the Berlin Heart EXCOR®, and found 57% of patients were able to achieve good outcomes (weaned or transplanted) with this number, decreasing to 27% in patients weighing <5 Kg (5). When the results from this study are examined more closely, it is clear that the patients <10Kg were not homogenous, with 26 (26.8%) patients having a diagnosis of CHD. The authors observed that for patients with no CHD and <10Kg, no pre-implant ECMO and normal bilirubin, 87.5% were successfully supported to HTx. However, this rate dropped to 30.8% in those with CHD, and even further for patients with CHD on ECMO and/or who had elevated bilirubin. These reported survival patterns remained true for those

<5Kg with a 66.7% success rate in children without CHD, who did not require pre-ECMO and had normal bilirubin; whereas, only 1/12 infants with CHD <5 Kg (n=13) survived to transplant (5). This is similar to our results in patients <5Kg, where the majority had single ventricle physiology and a survival rate of 44% at three months post VAD implant. These results are in contrast to children <10Kg with CM or myocarditis, where survival to HTx on VAD therapy has been reported to be as high as 91% (11). This is consistent with our observation of excellent survival on device therapy for small patients with CM.

This study had a number of limitations inherent to a retrospective analysis, especially with small patient numbers. Another major limitation identified during the study was the difference in patient cohorts supported by the two modes of MCS. ECMO was predominantly used as first line therapy in younger and smaller patients with a higher percentage of patients having single ventricle physiology. In addition, children <5Kg were left on ECMO for longer periods of time, likely secondary to the lack of available support options, increasing the risk of mortality as time on device increased. Moreover, as we did not know the reason for ECMO initiation, we could not account for the impact of the primary indication for ECMO, which may have influenced the difference in outcomes between the forms of MCS. Lastly, as time on VAD support prior to HTx is limited, conclusions cannot be drawn about long term outcomes while waiting. Therefore, when examining the results of previous studies and when designing analyses moving forward, it would be important to take these observations into consideration.

While this study confirms previous reports of the negative impact of ECMO on outcomes in small children listed for HTx, it has also begun to tease out key information in understanding the patients <10Kg that require MCS. Characterizing this patient population is essential for moving forward to aid in determining which treatment options will have the most impact for a particular diagnosis. The observations throughout this study speak to the tremendous need for the development of device options for these small patients, especially those with CHD. Supporting these children remains a challenge and there is an ongoing need for research and development of smaller pumps that are designed for the unique features of the pediatric population.

2.5 References

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2.6 Tables

Table 2.1: Demographics at Listing

Demographics at Listing	Cardiomyopathy (n=823)	Congenital Heart Disease (n=1226)	p-value
Male	368 (44.7)	701 (57.2)	<0.0001
White	523 (63.5)	844 (68.8)	0.01
Status 1A	498 (75.1)	968 (87.8)	<0.0001
Status 1B	123 (18.6)	82 (7.4)	<0.0001
PRA > 10	96 (18.9)	176 (24.4)	0.02
Ventilator at Listing	314 (40.1)	509 (43.2)	0.2
Inotropes at Listing	611 (74.6)	831 (68.0)	0.001
ECMO at Listing	73 (8.9)	88 (7.2)	0.2
ECMO after Listing	37 (5.4)	71 (6.4)	0.4
VAD at Listing	66 (8.0)	29 (2.4)	<0.0001
VAD after Listing	156 (22.8)	57 (5.1)	<0.0001
History of Surgery at Listing	67 (8.2)	930 (75.9)	<0.0001
History of Renal Insufficiency	21 (2.7)	64 (5.4)	0.004
Age (months) at Listing	7.0 ± 6.5	5.2 ± 6.4	<0.0001
Weight (Kg) at Listing	6.0 ± 2.1	5.1 ± 2.0	<0.0001
Patients with weight <5Kg	305 (37.1)	697 (56.9)	<0.0001
Serum Albumin (g/dL)	3.5 ± 1.6	3.3 ± 1.6	0.004
Bilirubin at Listing (mg/dL)	1.1 ± 2.0	1.8 ± 3.0	<0.0001
Creatinine at Listing (mg/dL)	0.4 ± 0.2	0.4 ± 0.5	0.01
Transplant Year	2014.1 ± 2.5	2014.4 ± 2.5	0.05
VAD: Ventricular Assist Device ECMO: Extracorporeal Membrane Oxygenation			

Table 2.2: Characteristics at Listing for Support Group

Characteristics at Listing	VAD (n=95)	ECMO (n=161)	Unsupported (n=1793)	p-value	VAD or ECMO at Listing (n=256)	VAD or ECMO after Listing (n=321)	p-value
Male	49 (51.6)	87 (54.0)	933 (52.0)	0.9	136 (53.1)	164 (51.1)	0.6
Primary Diagnosis				<0.0001			<0.0001
Cardiomyopathy/ Myocarditis	59 (62.1)	58 (36.0)	653 (36.4)		139 (54.3)	193 (60.2)	
Congenital Heart Disease	29 (30.5)	88 (54.7)	1109 (61.9)		117 (45.7)	128 (39.9)	
White	51 (53.7)	104 (64.6)	1212 (67.6)	0.02	155 (60.5)	202 (62.9)	0.6
Status 1A	63 (95.5)	141 (97.2)	1262 (81.2)	<0.0001	204 (96.7)	229 (85.8)	<0.0001
Status 1B	0 (0.0)	1 (0.7)	204 (13.1)	<0.0001	1 (0.5)	34 (12.7)	<0.0001
PRA > 10	21 (25.3)	24 (16.9)	452 (27.6)	0.02	21 (17.8)	38 (21.0)	0.5
Ventilator at Listing	58 (61.7)	138 (85.7)	627 (36.7)	<0.0001	196 (76.9)	145 (46.5)	<0.0001
Inotropes at Listing	57 (62.0)	123 (76.9)	1262 (70.5)	0.04	180 (71.4)	252 (78.5)	0.05
History of Surgery at Listing	32 (33.7)	83 (51.9)	882 (49.2)	0.009	115 (45.1)	107 (33.4)	0.0043
History of Renal Insufficiency	5 (5.5)	18 (11.5)	62 (3.6)	<0.0001	23 (9.3)	7 (2.4)	0.0004
Age (months) at Listing	8.6 ± 6.3	3.8 ± 4.8	6.0 ± 6.6	<0.0001	5.6± 5.8	6.6 ± 6.5	0.06
Weight (Kg) at Listing	6.5 ± 2.0	5.0 ± 2.2	5.5 ± 2.1	<0.0001	5.6 ± 2.3	5.8 ± 2.1	0.3
Patients with weight <5Kg	27 (28.4)	101 (62.7)	874 (48.7)	<0.0001	128 (50.0)	136 (42.4)	0.07
Serum Albumin (g/dL)	3.3 ± 0.7	3.1± 0.8	3.4 ± 1.6	0.03	3.2 ± 0.8	3.3 ± 0.7	0.02
Bilirubin at Listing (mg/dL)	0.9 ± 1.2	2.5 ± 4.2	1.4 ± 2.5	<0.0001	1.9 ± - 3.5	1.2 ± 2.0	0.006
Creatinine at Listing (mg/dL)	0.4 ± 0.2	0.5 ± 0.4	0.4 ± 0.4	<0.0001	0.5 ± 0.3	0.4 ± 0.2	<0.0001
Transplant Year	2014.2 ± 2.4	2014.3± 2.8	2014.2 ± 2.5	1.0	2014.3 ± 2.6	2014.5 ± 2.6	0.5
VAD: Ventricular Assist Device; ECMO: Extracorporeal Membrane Oxygenation							

Table 2.3: Characteristics at Listing for Support Group for Congenital Heart Disease Patients

Characteristics at Listing	VAD (n=29)	ECMO (n=88)	Unsupported (n=1109)	p-value	VAD or ECMO at Listing (n=117)	VAD or ECMO after Listing (n=128)	p-value
Male	16 (55.2)	50 (56.8)	635 (57.3)	1.0	66 (56.4)	79 (61.7)	0.4
White	22 (75.9)	56 (63.6)	766 (69.1)	0.4	78 (66.7)	87 (68.0)	0.8
Single Ventricle	7 (24.1)	40 (45.5)	674 (60.8)	<0.0001	47 (40.2)	77 (60.2)	0.002
Status 1A	19 (95.0)	78 (98.7)	871 (86.8)	0.005	97 (98.0)	108 (93.1)	0.09
Status 1B	0 (0.0)	0 (0.0)	82 (8.2)	0.01	0 (0.0)	6 (5.2)	0.02
PRA > 10	6 (24.0)	9 (11.7)	297 (29.2)	0.004	15 (14.7)	29 (25.0)	0.1
Ventilator at Listing	20 (71.4)	78 (88.6)	411 (38.7)	<0.0001	98 (84.5)	60 (48.4)	<0.0001
Inotropes at Listing	16 (59.3)	66 (75.9)	749 (67.6)	0.2	82 (71.9)	94 (73.4)	0.8
History of Surgery at Listing	25 (86.2)	80 (90.9)	825 (74.5)	0.001	105 (89.7)	93 (72.7)	0.0007
History of Renal Insufficiency	2 (7.1)	10 (11.6)	52 (4.8)	0.02	12 (10.5)	4 (3.3)	0.03
Age (months) at Listing	9.0 ± 6.4	3.1 ±4.3	5.3 +/- 6.5	<0.0001	4.5 +/- 5.5	5.1 ± 5.7	0.5
Weight (Kg) at Listing	6.0 ± 2.1	4.4 ±1.9	5.2 +/- 2.0	0.0001	4.8 +/- 2.0	5.2±2.0	0.1
Patients with weight <5Kg	12 (41.4)	65 (73.9)	620 (55.9)	0.001	77 (65.8)	71 (55.5)	0.1
Serum Albumin (g/dL)	3.3 ± 0.5	3.0 ± 0.7	3.4 ± 1.6	0.1	3.1 ± 0.7	3.2 ±0.7	0.3
Bilirubin at Listing (mg/dL)	0.8 ± 0.8	3.0 ± 5.0	1.7 ±2.7	0.0002	2.5 ± 4.5	1.8 ± 2.5	0.1
Creatinine at Listing (mg/dL)	0.4 ± 0.2	0.5 +/- 0.3	0.4 ±0.5	0.1	0.5 ± 0.3	0.4 ± 0.2	0.0004
Transplant Year	2015.3 ± 2.3	2014.9 ±2.6	2014.3 ± 2.5	0.1	2015.0 ± 2.5	2015.0 ±2.6	1.0
VAD: Ventricular Assist Device; ECMO: Extracorporeal Membrane Oxygenation							

Table 2.4: Characteristics at Listing for Support Group for Cardiomyopathy/Myocarditis Patients

Characteristics at Listing	VAD (n=66)	ECMO (n=73)	Unsupported (n=684)	p-value	VAD or ECMO at Listing (n=117)	VAD or ECMO after Listing (n=128)	p-value
Male	33 (50.0)	37 (50.7)	298 (43.6)	0.3	70 (50.4)	85 (44.0)	0.3
White	29 (43.9)	48 (65.8)	446 (65.2)	0.003	77 (55.4)	115 (59.6)	0.4
Status 1A	44 (95.7)	63 (95.5)	391 (71.0)	<0.0001	107 (95.5)	121 (80.1)	0.0003
Status 1B	0 (0.0)	1 (1.5)	122 (22.1)	<0.0001	1 (0.9)	28 (18.5)	<0.0001
PRA > 10	15 (25.9)	15 (23.1)	155 (25.0)	0.9	30 (24.4)	43 (25.7)	0.8
Ventilator at Listing	38 (57.6)	60 (82.2)	216 (33.5)	<0.0001	98 (70.5)	85 (45.2)	<0.0001
Inotropes at Listing	41 (63.1)	57 (78.1)	513 (75.3)	0.07	98 (71.0)	158 (81.9)	0.02
History of Surgery at Listing	7 (10.6)	3 (4.2)	57 (8.3)	0.4	10 (7.2)	14 (7.3)	1.0
History of Renal Insufficiency	3 (4.8)	8 (11.3)	10 (1.5)	<0.0001	11 (8.2)	3 (1.7)	0.007
Age (months) at Listing	8.5 ± 6.3	4.7 ± 5.1	7.1 ± 6.6	0.002	6.5 ± 6.0	7.6 ± 6.9	0.1
Weight (Kg) at Listing	6.8 ± 1.9	5.7 ± 2.4	6.0 ± 2.1	0.008	6.2 ± 2.2	6.2 ± 2.1	0.8
Patients with weight <5Kg	15 (22.7)	36 (49.3)	254 (37.1)	0.005	51 (36.7)	65 (33.7)	0.6
Serum Albumin (g/dL)	3.4 ± 0.8	3.2 ± 0.8	3.6 ± 1.7	0.1	3.3 ± 0.8	3.5 ± 0.7	0.07
Bilirubin at Listing (mg/dL)	0.9 ± 1.3	1.9 ± 2.7	1.0 ± 2.0	0.002	1.4 ± 2.2	0.9 ± 1.3	0.006
Creatinine at Listing (mg/dL)	0.4 ± 0.2	0.5 +/- 0.4	0.3 ± 0.2	<0.0001	0.5 ± 0.4	0.4 ± 0.2	0.0003
Transplant Year	2013.9 +/- 2.4	2013.8 ± 2.8	2014.1 +/- 2.5	0.6	2013.9 +/- 2.6	2014.3 +/- 2.6	0.2

VAD: Ventricular Assist Device
ECMO: Extracorporeal Membrane Oxygenation

Table 2.5: Type of Congenital Heart Disease

Type of Congenital Heart Disease	Yes (n)	Yes (%)
Arch Hypoplasia/Interruption/Hypoplasia	34	0.12
Atrial Septal Defect/Ventricular Septal Defect	117	0.1
Atrioventricular Discordance	0	0
Bilateral Superior Vena Cava (SVC)	4	0.02
Complete Atrioventricular SeptalDefect/AV Canal	97	0.08
Congenitally Corrected Transposition	17	0.01
Coronary Anomaly	34	0.05
Dextrocardia	7	0.03
Double Inlet Left Ventricle	17	0.02
Ebsteins Anomaly	24	0.02
Heterotaxy	32	0.05
Hypoplastic Left Heart	578	0.47
Hypoplastic Right Ventricle Not Otherwise Specified	40	0.05
Interrupted Inferior vena cava	1	0
Left SVC (no right SVC)	0	0
Left Ventricular Outflow Tract Obstruction / Aortic Stenosis	74	0.08
Mitral Stenosis	21	0.08
Right Aortic Arch	0	0
PDA	1	0
Pulmonary Atresia [with complex heart disease, not intact septum or Tetralogy of Fallot (TOF)]	10	0.04
Pulmonary Atresia with Intact Ventricular Septum	197	0.16
Situs Inversus	0	0
Total Anomalous Pulmonary Venous Return	18	0.02
Partial Anomalous Pulmonary Venous Return	1	0
TOF/TOF Variant/Double outlet right ventricle/Right ventricular outflow tract obstruction	90	0.07
Transposition of the Treat Arteries (d-TGA)	66	0.05
Tricuspid Atresia	31	0.04
Truncus Arteriosus	12	0.01
Unknown	5	0.11
Other	44	0.04

Table 2.6: Adjusted Risk of Mortality on the Waitlist by Diagnosis and MSC Use*

Variable	Hazard Ratio	95% Confidence Interval	p-value
Parametric Hazard Modeling Results for Congenital Heart Disease			
Race (white)	0.76	0.60-1.0	0.04
List year (since 2010)	0.92	0.88-0.96	0.0004
ECMO	4.40	3.30-5.85	<0.0001
VAD	2.46	1.65-3.66	<0.0001
Weight at Listing (kg)	0.94	0.88-1.00	0.05
Status 1A at Listing	2.04	1.27-3.28	0.003
Ventilator at Listing	1.54	1.18-2.01	0.001
Parametric Hazard Modeling Results for Cardiomyopathy			
ECMO	3.48	2.16-5.60	<0.0001
VAD	1.83	1.18-2.86	0.008
Ventilator at Listing	1.79	1.20-2.68	0.005
Parametric Hazard Modeling Results for ECMO			
List year (Since 2010)	0.89	0.82-0.96	0.002
CHD	2.7	1.75-4.16	<0.0001
Parametric Hazard Modeling Results for VAD			
Weight at Listing LN (kg)	0.324	0.17-0.62	0.0006
CHD	2.19	1.31-3.66	0.003

2.7 Figures

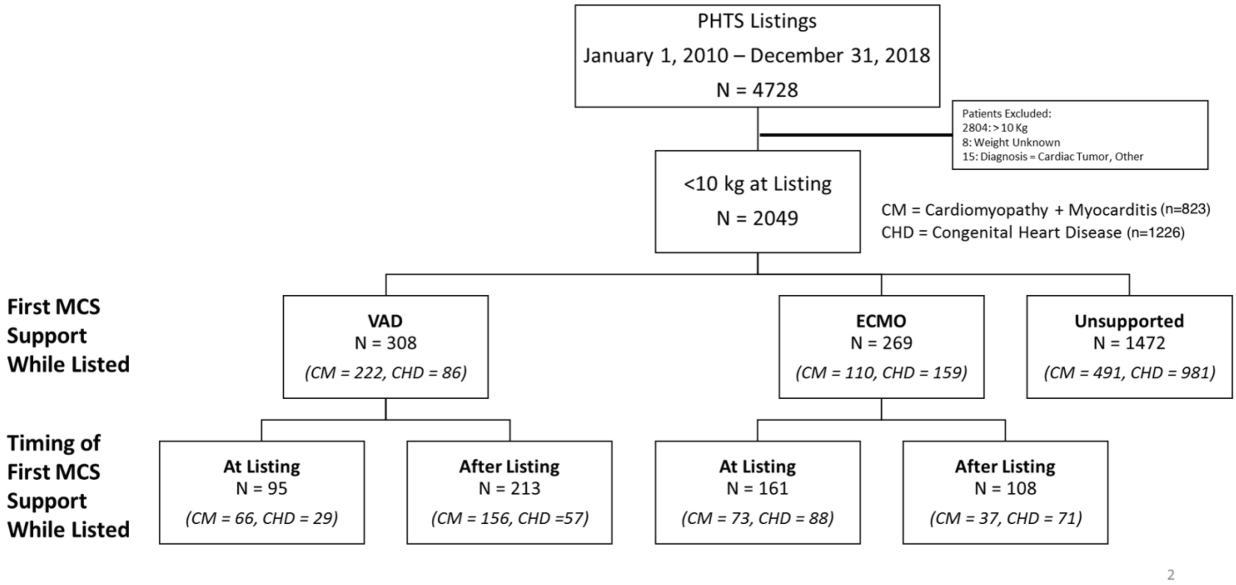

Figure 2.1: Flow chart outlining the cohort of children <10Kg and divided by primary diagnosis, MCS type and time of initiation of support.

PHTS: Pediatric Heart Transplant Society; VAD: ventricular assist device; ECMO: extracorporeal membrane oxygenation; CM: cardiomyopathy; CHD: congenital heart disease.

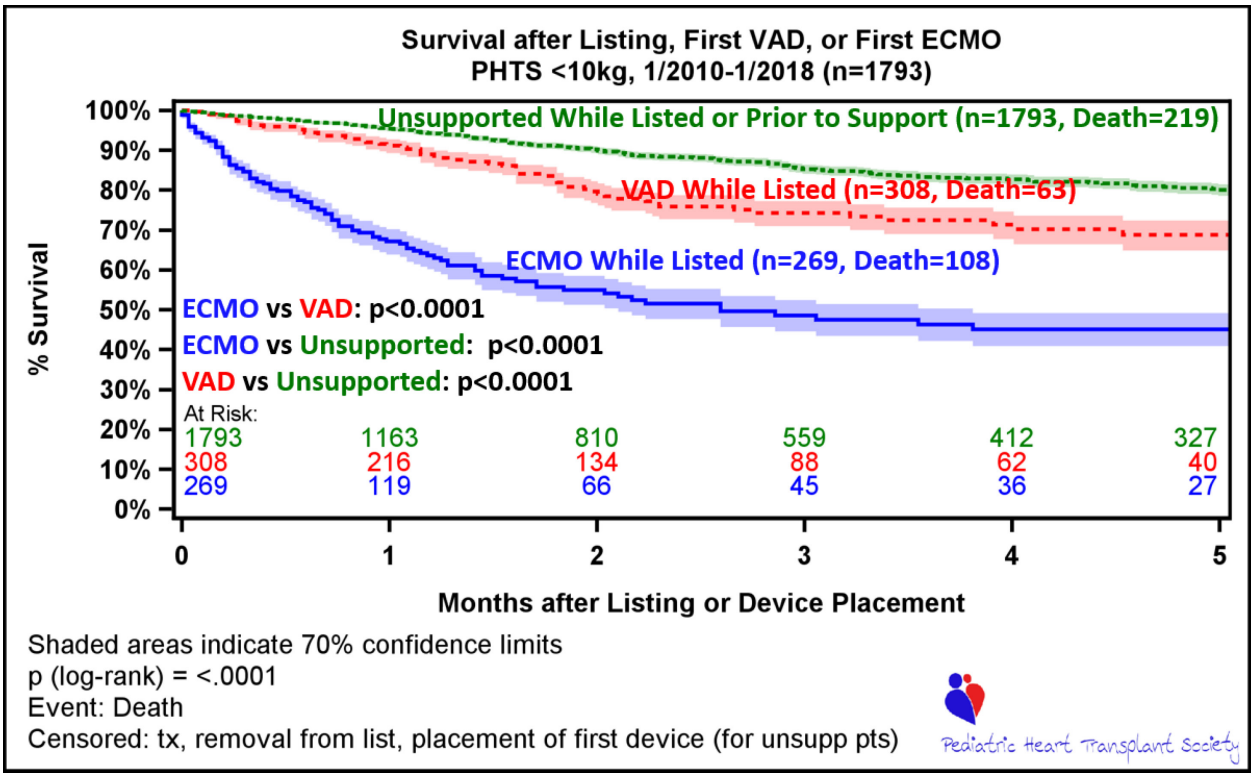

Figure 2.2: Waitlist survival, stratified by absence of support, VAD while listed, and ECMO while listed.

Time 0 is time of listing for unsupported patients, who are followed to the event death or censored at transplant, removal from list, or at time of first device (ECMO or VAD). The lower two curves depict survival while on first device, either ECMO or VAD. Time 0 for patients on device (ECMO or VAD) is time of listing (if patient on device at listing) or time implant of first device following listing. Patients in this cohort are censored at transplant or removal from list. VAD: ventricular Assist device; ECMO: extracorporeal membrane oxygenator; Tx: transplant; unsupp pts: unsupported patients.

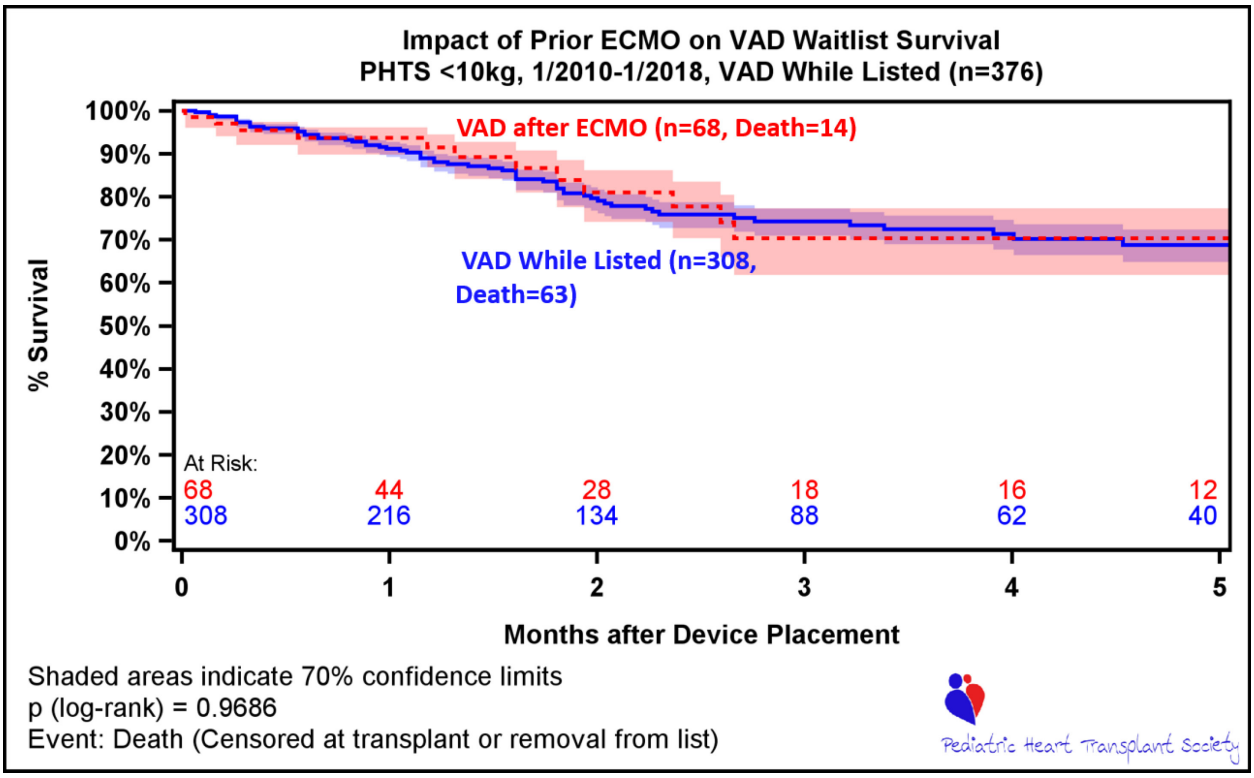

Figure 2.3: Survival after VAD implant on waitlist, stratified by VAD as initial device vs. VAD following ECMO.

Time zero is device placement or listing (if device placed prior to listing). VAD: ventricular Assist device; ECMO: extracorporeal membrane oxygenator.

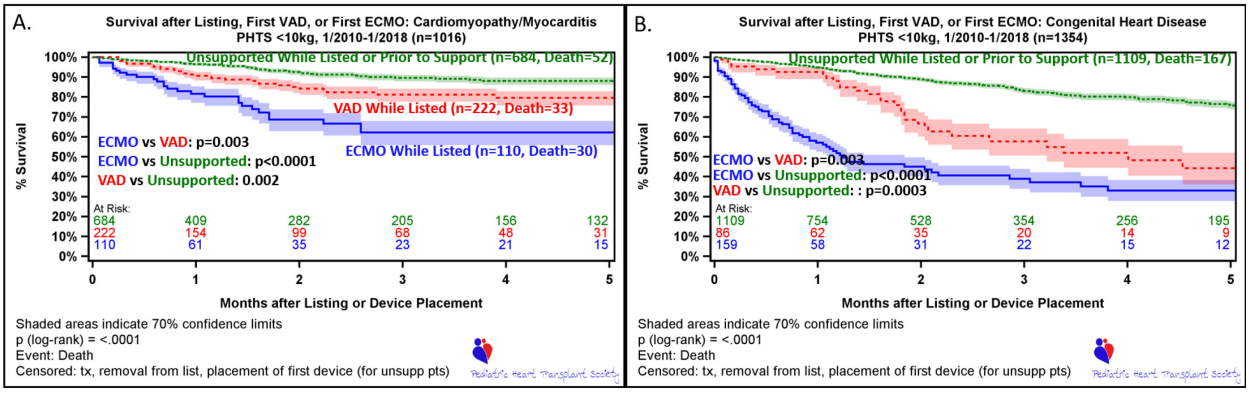

Figure 2.4: Waitlist survival, stratified by absence of support, VAD while listed, and ECMO while listed.

Panel A includes patients with cardiomyopathy/myocarditis and Panel B includes patients with CHD. Time 0 is time of listing for unsupported patients, who are followed to the event death or censored at transplant, removal from list, or at time of first device (ECMO or VAD). The lower two curves depict survival while on first device, either ECMO or VAD. Time 0 for patients on device (ECMO or VAD) is time of listing (if patient on device at listing) or time implant of first device following listing. Patients in this cohort are censored at transplant or removal from list. VAD: ventricular Assist device; ECMO: extracorporeal membrane oxygenator; Tx: transplant; unsupp pts: unsupported patients.

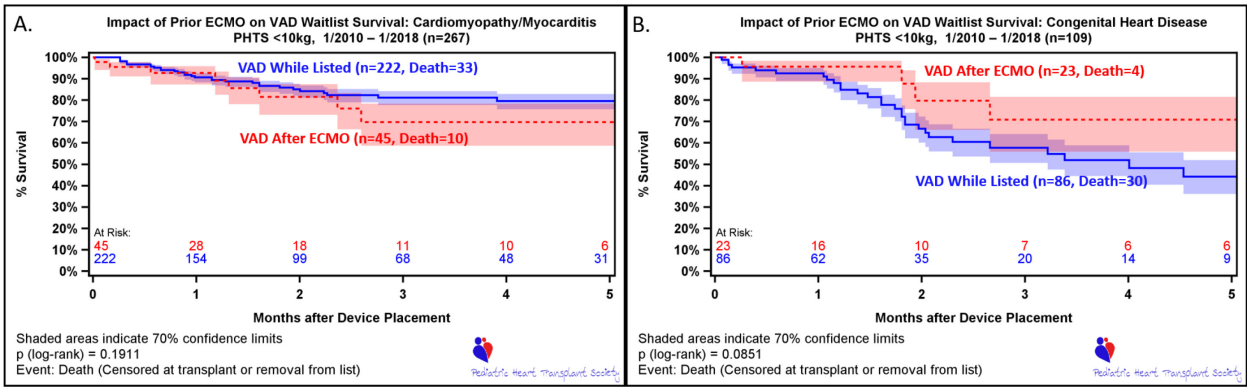

Figure 2.5: Survival after VAD implant on waitlist, stratified by VAD as initial device vs. VAD following by ECMO.

Time zero is device placement or listing (if device placed prior to listing). Panel A displays this information for Cardiomyopathy/Myocarditis patients and Panel B patients with Congenital Heart Disease. VAD: ventricular Assist device; ECMO: extracorporeal membrane oxygenator.

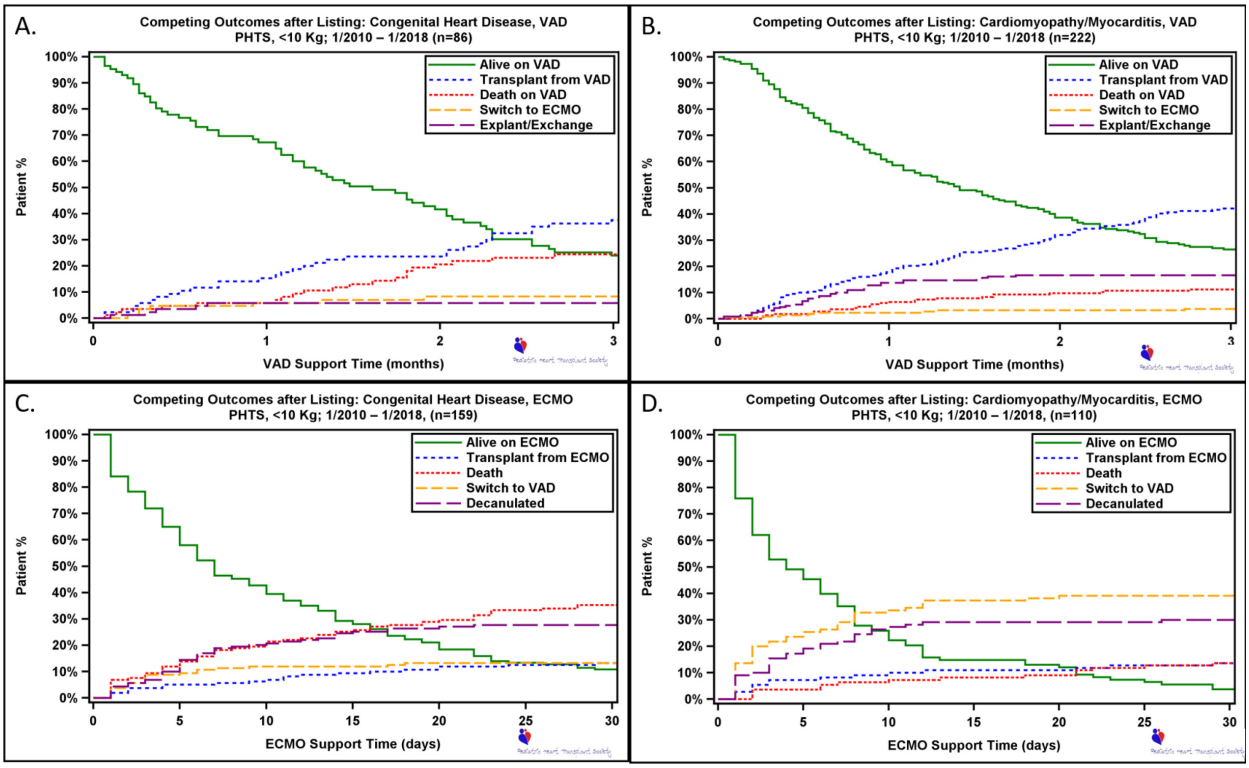

Figure 2.6: Competing Outcomes Depictions for mutually exclusive outcomes after first MCS.

Panels: A: VAD support in Congenital Heart Disease patients; B: ECMO support in Congenital Heart Disease patients; C: VAD support in Cardiomyopathy/Myocarditis patients and D: ECMO support in Cardiomyopathy/Myocarditis patients. VAD: ventricular Assist device; ECMO: extracorporeal membrane oxygenator

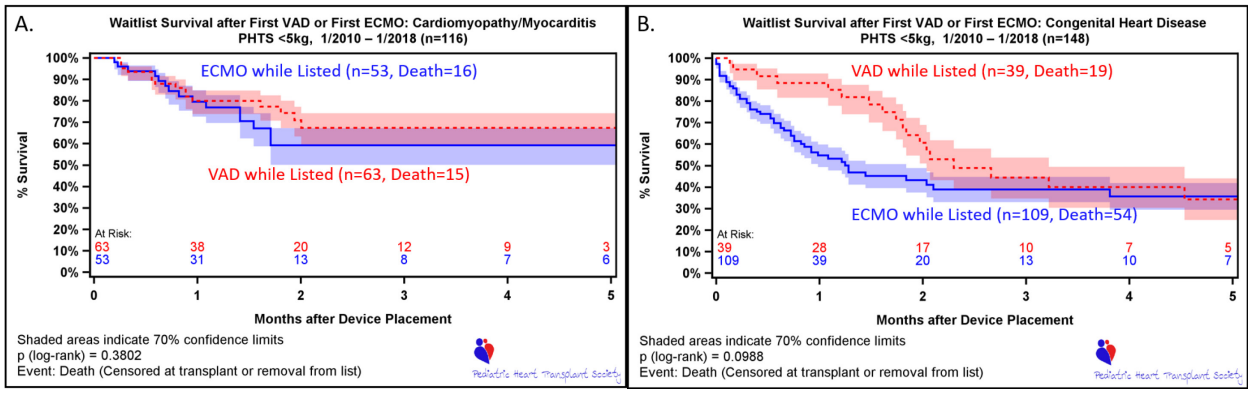

Figure 2.7: Waitlist survival after first MCS, stratified by VAD vs. ECMO in patients weighing <5Kg.

Time zero is device placement or listing (if the device is placed prior to listing). Panel A: Cardiomyopathy/Myocarditis patients; Panel B: Congenital Heart Disease patients. VAD: ventricular assist device; ECMO: extracorporeal membrane

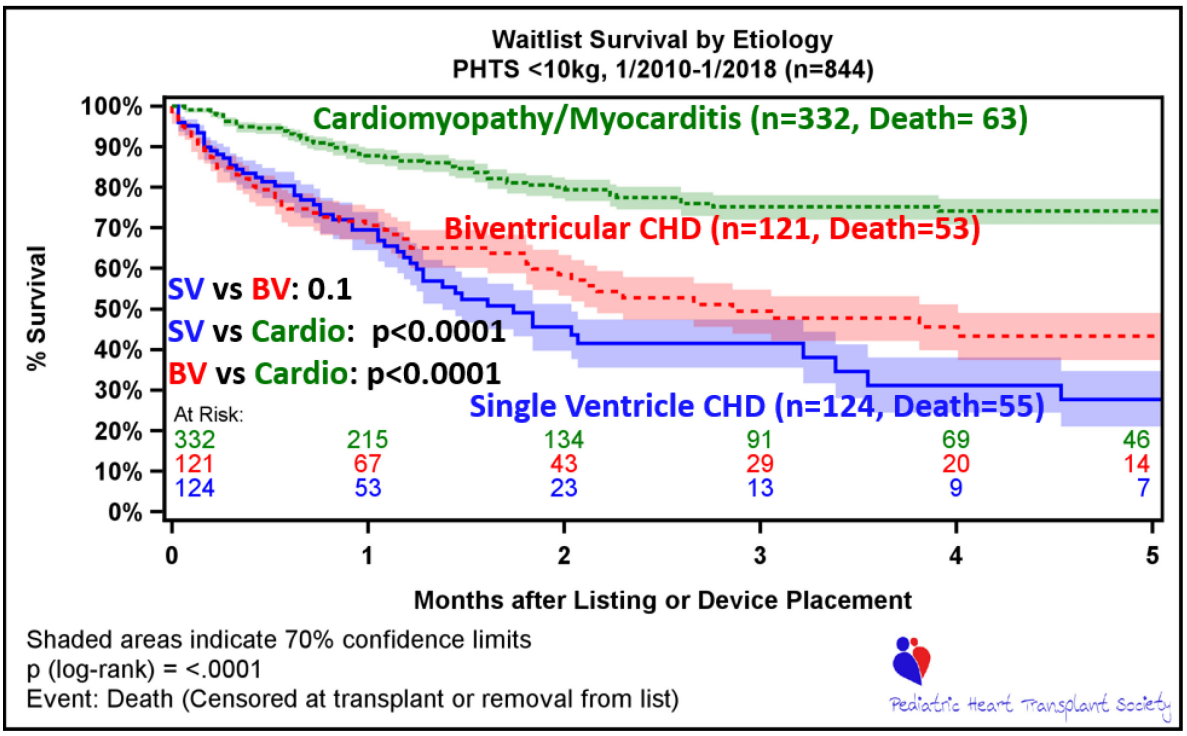

Figure 2.8: Supplemental Figure 1: Waitlist survival following first device placement for children with CM, Biventricular CHD, and Single Ventricle CHD.

Time zero is device placement or listing (if the device is placed prior to listing). VAD: ventricular assist device; ECMO: extracorporeal membrane oxygenation; CM: cardiomyopathy; CHD: congenital heart disease.

Supplemental Information 2.1: Pediatric Heart Transplant Society Sites

Arkansas Children's Hospital

Boston Children's Hospital

University of California, San Francisco-Benioff Children's Hospital

Cleveland Clinic Children's

Cincinnati Children's Hospital Medical Center

Nationwide Children's Hospital

Cardinal Glennon Children's Medical Center

Children's Hospital of Los Angelos

Children's Hospital of Pittsburgh of UPMC

Children's Hospital of Wisconsin

Ann & Robert H. Lurie Children's Hospital of Chicago

University of Texas, Children's Medical Center

Children's Mercy Hospital and Clinics

Children's National Medical Center

The Children's Hospital of Philadelphia

Columbia University-Morgan Stanley Children's Hospital of New York Presbyterian

Duke Children's Hospital

Children's Healthcare of Atlanta

Freeman Hospital, Newcastle upon Tyne

University of Florida, Shands Hospital

Great Ormond Street Hospital for Children

Hospital for Sick Children

Riley Hospital for Children

Joe DiMaggio Children's Hospital

Johns Hopkins Hospital

University of Miami, Jackson Memorial Hospital

Levine Children's Hospital- Atrium Health

Loma Linda University Children's Hospital

Norton Children's Hospital

University of Michigan, CS Mott Children's Hospital

University of Minnesota Masonic Children's Hospital

Children's Hospital at Montefiore

Medical University of South Carolina

Mount Sinai Medical Center

Nemours Cardiac Center

Children's Hospital and Medical Center

Phoenix Children's Hospital

Primary Children's Hospital

UC San Diego, Rady Children's Hospital

Seattle Children's Hospital

St. Louis Children's Hospital

Lucile Packard Children's Hospital at Stanford

Texas Children's Hospital

Children's of Alabama

Mattel Children's Hospital

Children's Hospital Colorado

University of Iowa Children's Hospital

UNC Children's Hospital

University of Alberta

Johns Hopkins All Children's Hospital

University of Virginia Medical Center

Monroe Carell Jr. Children's Hospital at Vanderbilt

Supplemental Information 2.2: Covariates for Hazard Model

- Etiology
- Race
- Sex
- Age at Listing, months (natural log, squared)
- Weight at Listing, Kg (natural log, squared)
- Ventilator status at Listing
- Status at Listing
- Inotropes at Listing
- History of Surgery
- History of Renal Insufficiency
- Years since 2010
- Creatinine (mg/dL)
- Bilirubin (mg/dL)
- Single Ventricle Congenital Heart Disease
- ECMO
- VAD

3 Chapter 3: WORLDWIDE EXPERIENCE WITH THE HEARTWARE HVAD® IN PEDIATRIC PATIENTS

Conway J, Miera O, Adachi I, Maeda K, Eghtesady P, Henderson HT, et al. Worldwide Experience of a Durable Centrifugal Flow Pump in Pediatric Patients. Semin Thorac Cardiovasc Surg. 2018; 30(3):327–35.

3.1 Background

The outcome of end stage heart failure in children has significantly improved due to the introduction of ventricular assist devices (VADs). While in the past pulsatile VADs have been the predominant form of long-term support, the recent introduction of adult continuous flow devices into pediatric practice has further expanded the treatment options for children with end stage heart failure. The continuous flow pumps that have gained the most attention in pediatrics have been the Heartmate II™ (St. Jude Medical, St.Paul, MN) and the HeartWare HVAD™system (HeartWare Inc, Miami Lakes, FL). These devices are small enough to implant in larger children, allow for hospital discharge, and are safe and effective in adult patients (1,2). The Heartmate II™ is typically reserved for adolescent patients, whereas the HeartWare HVAD™ system can be used in a wider range of children with reports of implants in children as small as 15 Kg (3-8).

An understanding of the outcomes of continuous flow pumps in children is still in the early stages, with most reports focused around a single center or small multicenter results. Recently, the Pediatric Interagency Registry for Mechanical Circulatory Support (PediMACS) published results for all continuous-pumps in patients implanted in the United States (9). There were 109 patients with a median age at implant of 15 years (0.6-18.9) and weight of 62 kg (16-141Kg). The median support time in this cohort was three months (0.1-21 months) with 45% of the patients discharged to home (9). At six months post implant, 61% of patients had been transplanted, 31% had ongoing VAD support and 8% had died on the device. While this paper did not differentiate between device types, it did suggest excellent outcomes in this US cohort.

Device specific results for the HeartWare HVAD™ system have been limited by small patient numbers. However, all the publications to date have suggested encouraging results in the pediatric population, including the ability to discharge patients home regardless of age and size (3-10).

While the published experience with the HeartWare HVAD™ system in children is limited, there are many more patients that have been implanted with this device throughout the world (verbal communication with the company). These patients represent an important cohort of children that could improve our knowledge of outcomes, enable comparison between outcomes in North America and the rest of the world and improve patient management and further education. Therefore, the primary objective of this study was to

determine the clinical outcomes of children (age <18 years) supported with the HeartWare HVAD™ system from the global pediatric community.

3.2 Methods

This was a retrospective review of pediatric patients (<18 years) implanted with a HeartWare HVAD® system. Centers throughout the world were identified based on previous publications and our collective knowledge of the various pediatric VAD centers. Notifications about the project were sent out to centers by email. In addition, a notice announcing the study was sent to pediatric implanting centers identified by HeartWare Inc. with instructions on how to contact the primary investigator. Research ethics board approval for the project occurred at the site of the primary investigator and at the individual sites depending on the local requirements.

3.2.1 Data Collection

The survey was designed with a minimal data set to reduce the time commitment from each center in order to encourage participation (See Appendix). Questionnaires were sent out in April 2015 and collected between May 2015 and May 2016. Patients were eligible to be included if they were <18 years at the time of HeartWare HVAD™ system implant and if the implant occurred prior to April 1, 2016. Data were collected at each individual site by the site research team from the patient charts. All patients were included in the study regardless of the duration of follow up. The duration of follow-up was calculated from implant date to the day that the individual center collected their data. Study data were collected and managed using REDCap electronic data capture tools hosted and supported by the Women and Children's Health Research Institute at the University of Alberta (11)

3.2.2 Outcomes Analysis

The primary outcomes of interest are post-implantation clinical events, including death, heart transplant, and wean for recovery. The primary outcome was measured by the month-to-first-event following VAD implantation. A patient was right-censored if he/she had not experienced any clinical event of interest by the end of follow-up. In addition, we considered the post-VAD discharge status as a secondary outcome, which was measured by the days to discharge following VAD implantation.

Outcomes were also examined for those patients with the value of body surface area ≤1 vs. >1 m^2 at the time of implant. This cut-off was chosen, as traditionally, these patients would have been implanted with a pulsatile pump due to their size.

3.2.3 Statistical Method

Data were described using summary statistics. For clinical characteristics, continuous variables were summarized using median and interquartile range (IQR). Between-group differences were assessed using Wilcoxon rank-sum tests. Dichotomous and polytomous variables were summarized in terms of

frequencies and proportions, and Fisher's exact tests were used to assess the between-group differences.

In the descriptive outcome analysis, both primary and secondary time-to-event outcomes were analyzed using competing risk models, the results of which were presented in terms of the cumulative proportion of patients. Comparison between two BSA groups for death on device was evaluated using Gray's tests for competing risk models.

Following the index VAD implantation, some (n= 24) patients with LVAD implantation were given temporary RVAD support, and some had the index VAD exchanged (n= 8). To assess and quantify the association between primary outcome and RVAD support and device exchange, we used multivariable cause-specific hazard regression models for post-VAD mortality and cardiac transplant. We did not conduct a cause-specific hazard regression for recovery because of the insufficient number of patients with this clinical event.

The multivariable regression models included temporary RVAD support and pump exchange as time-varying risk factors as well as site- and patient-specific clinical characteristics as covariates: the year and region of implant, age, sex, body surface area (≤1 vs. >1 m^2), previous sternotomy, the presence of congenital heart disease and cardiomyopathy (i.e. no vs. dilated vs. other cardiomyopathies). The regression model only considered patients with LVAD implemented (n= 190) because they were eligible for temporary RVAD support. Furthermore, the proportionality assumption was assessed using Schoenfeld residuals, and a model with time-dependent coefficients is considered should there be strong evidence against the proportionality assumption.

The descriptive analysis was conducted using SAS v9.4, and the competing risk analysis was conducted using R *v*3.3.2.

3.3 Results

3.3.1 Patient Population

Two hundred and five patients from 35 sites and 12 countries were included in this study. Of the implanting sites, 20 were from North America (n=123), 10 from Europe (n=57) and 5 (n=25) from other sites around the world (Australia, Turkey, Israel, Japan and Egypt). The total number of implants per site varied from <5 (18 sites) to 5-9 (10 sites) and 10-20 (7 sites). The majority of the implants occurred in a site that identified themselves as a pediatric center (93%). Implants occurred between 2009 and 2016, with the majority of implants occurring within or after 2014 (67%).

Table 2.1 outlines the clinical characteristics at implant. The median (IQR) age of implant was 13.1 (9.8 - 15.8) years, with the youngest being 2 years old. The median (IQR) weight was 42 (28 - 60) kg, with the smallest patient weighing 10 kg. Over half of the implants occurred in males (61%), with the most common diagnosis being isolated cardiomyopathy (n=168; 79%). Twenty-nine (14%) patients had a diagnosis of congenital heart disease; among those, 18 (62%) patients having a biventricular circulation. Of note, six of the above (3%) congenital patients also had a diagnosis of cardiomyopathy. Of those patients with single ventricle physiology, their weight ranged from 20-75Kg, and all implants occurred in a pediatric center. In addition, there were 10 patients with myocarditis, 3 who were post-transplant, and 1 with idiopathic pulmonary hypertension (n=14).

There were 50 patients (24.4%) who had a BSA ≤1m^2 at the time of implantation. The median age of this group was 7.3 (6-9.1) years, with the most common etiology being dilated cardiomyopathy (Table 2.2). The majority of the patients were implanted at a pediatric center (n=49, 98%). The differences between groups based on BSA are outlined in Table 2.2.

3.3.2 Implant Procedure

The majority of HVAD® systems implanted were LVADs (n=189; 92.2 %,) with 4 (2%) patients having a biventricular HVAD® and 1 (0.5%) patient a single right sided HVAD. In addition, there were 11 patients with single ventricle physiology that had the inflow cannula positioned in either a systemic ventricle or common atrium. For those patients ≤1m^2, LVAD support was the most common form of support (n=45, 90%).

Following implantation, 24 (12%) patients required temporary RVAD support. The most common devices used for temporary RVAD support were the St. Jude Centrimag/Pedimag (n=13), followed by the Marquet Rotaflow (n=3) and ECMO (n=3). There were 4 additional devices for the 5 other implants (Berlin Heart EXCOR, CardioAssist, Medos DP3 and a combination of devices). The majority of the RVAD support was implanted within the first 4 days following LVAD implantation (n=22, 91.7%), with only 2 patients requiring RVAD after 40 days of support. Temporary RVAD support was required for a median duration of 12 (IQR 6 - 32) days. Four (2%) patients were still on RVAD support at the time of transplant or death. There was no difference in the need for temporary RV support between those ≤1m^2 vs. >1m^2 (14% vs. 11%, p=0.67).

3.3.3 Duration of Support

There was no significant difference in the duration of support between North American centers compared to the other centers [91 (46 - 211) vs. 81 (38 - 223), p=0.53]. For all patients, the median (IQR) duration of VAD support was 86 (45 – 215) days. The longest duration of support was 1642 days. In those patients with single ventricle physiology, the median (IQR) duration of support was 80 days (37 – 165), with the longest duration being 371 days.

3.3.4 Outcomes

Figure 2.1 shows the cumulative proportion of patients with a clinical event using a competing risk analysis for the time to the first event following VAD implantation. Based on the estimated curves, at 6 months post implant, 51.5% of the patients had undergone a transplant, 9.9% had died, 1.6% had been explanted for recovery and 37.1% remained on the VAD. By 12 months, the proportion who underwent transplant was 65.4%, 10.7% had died, 3.2% were explanted for recovery and 20.8% remained on the device. The majority of deaths on support occurred in the first 3 months. The causes of death are listed in Table 2.4, with multi-organ failure being the most common etiology.

3.3.5 Specific Patient Population

The outcomes of patients with hypertrophic cardiomyopathy (HCM) revealed that of the 6 patients, 5 underwent HTx and one died on support. For the 6 restrictive cardiomyopathy patients, 3 underwent HTx, 1 patient died on device, another died following a switch to a different pump type due to inadequate support and one remained on device at the time of data collection. In the single ventricle population (n=11), who had a median duration of follow-up of 56.5 days (33.3-196), 54.5% (n=6) patients were transplanted, 9.1% had died (n=1) and the rest (n=4) continued on support. The overall outcomes based on BSA are displayed in Figures 2.2 and 2.3. Figure 2.2 shows no difference in the cumulative proportion of patients receiving a transplant between the two groups (p=0.4). In addition, there was not a statistically significant difference at 12 months in the proportion of patients who died when the smaller patients were compared to those >1m^2 (14.8% vs. 9.4%, p=0.25) (See Figure 2.3).

3.3.6 Risk Factor Analysis

The risk factor analysis for mortality is summarized in Table 3. The univariable analysis shows that both implantation in a pediatric center and the need for a temporary RVAD increased the risk of a clinical event. A closer examination of the data showed that 97% of the temporary RVADs were implanted at a pediatric center and therefore, this parameter was felt not to be suitable for multi-variable analysis and was excluded from the model. As a result, only temporary RVAD was considered in the multivariable risk factor analysis. The results of the multivariable risk factor analysis show that the use of a temporary RVAD was associated with a substantial increase in post-VAD mortality [HR 10.65, (CI 2.53-44.8), p=0.001] as was the need for a pump exchange [HR 7.9, (CI 1.8-34.2), p=0.006]. For those patients requiring a temporary RVAD, the overall mortality was higher 25% (n=6/24) and this number was the same for patients requiring an exchange (n=2/8). Table 4 reveals no specific association with any of the risk factors examined and the likelihood of transplantation.

3.3.7 Discharge

Fifty-four percent (n=111) of patients were discharged home after VAD implantation following a median duration of hospital stay of 40 (IQR 28 – 71) days (Figure 4). By 120 days post implant, 55% of patients had been discharged, 35.5% had been transplanted without discharge and 9.4% had died prior to discharge. Three percent of patients remained hospitalized 240 days post-implant. Forty five percent

(5/11 patients) with single ventricle physiology were discharged, with the median (IQR) duration of hospital stay before discharge being 53 days (26-70). Fewer patients were discharged in the patients with a BSA ≤ 1m^2 compared to larger patients at 120 days post implant, but this difference was not statistically significant (48.1% vs. 56.8%, p=0.12). Discharge from the hospital was associated with older age, and every one-year increase in age increased the likelihood of discharge by 8.1% (HR 1.081 [95th CI: 1.042, 1.121], p<0.001).

A majority of patients were supported on their original device, with only eight (4%) patients requiring a device exchange. None of the single ventricle patients underwent a device exchange. The reason for the exchange was pump thrombosis in 6 patients and inadequate support in 2—those with inadequate support were switched to a different device. Two of the patients who underwent a device exchange eventually died, 4 underwent a transplant, one remained on the device and the last patient remained on an alternative form of mechanical support.

3.4 Discussion

Continuous flow VAD use in children has increased since the introduction of the HeartWare HVAD® system due to its size profile. Despite the introduction of this new technology to pediatrics and the potential differences in management that may occur between centers, short and medium term survival outcomes are excellent with no major difference based on geography.

The majority of patients implanted with this device were larger patients with dilated cardiomyopathy. However, there were some exceptions in this cohort, the youngest patient being 2 years of age and approximately 24% had a BSA ≤.1m^2. This trend to implant in smaller patients has been reported in previous studies with reasonable survival despite a number of morbidities (8). Neither age nor size were found to be associated with mortality in this international cohort. However, although there was no statistically significant difference in survival between the two BSA categories, there may be a trend towards worse outcomes in the smaller children, which did not reach significance given the sample size and the potential for a type II error. In addition, these smaller patients may represent a more complex patient population, as reflected in this series by the higher proportion of patients with a previous sternotomy and differences in underlying etiology. While this study was not designed to compare the outcomes to other devices or trials, given differences in patient cohorts and device management, we can utilize previous findings to help benchmark acceptable survival outcomes. The results from the Berlin Heart EXCOR® trial, showed through competing outcomes that mortality in the overall cohort (n=206) was 26% at 12 months and in the compassionate cohort was 36% at 12 months The smaller patients (≤1m^2) in this analysis has a 12 month mortality rate of 14.8% (12). We recognize that this comparison is flawed given the lack of matching between the cohorts, but this comparison does provide some guidance as to acceptable outcomes in this patient population.

Besides patients with cardiomyopathy, there was a small percentage of patients with congenital heart disease, including individuals with single ventricle physiology. Implantation in the single ventricle patients occurred either in the systemic ventricle or atrium. Just under half of these patients with single ventricle physiology were discharged, with only one patient dying on support and four still on support at the time of data entry. This analysis suggests that good results may be achievable, but further work is required to understand which patients with failing single ventricle physiology actually benefit from this technology.

The majority of implants were LVADs, as in most reported series on this subject, with only 4 patients with BIVAD HVAD®. Of these four BIVAD patients, two were transplanted, one died and one continued on the devices, with only one patient achieving discharge. While BIVAD HVAD® support was rare, the use of a temporary RVAD support was seen in just over 10% of the patients. Adult studies have shown that RV failure post LVAD insertion carries a high degree of morbidity and mortality(13). In addition, patients who have a temporary RVAD placed at the time of implantation have a more favourable outcome than those who are implanted later in the post-operative period (1,14). The need for temporary right heart support was found to be the only significant factor associated with mortality in this study cohort. This increased the risk of mortality over four fold. The identification of patients with right heart failure who will struggle post LVAD insertion in the pediatric population remains challenging, with a paucity of available data. Prediction models for RV failure post LVAD insertion do exist in the adult literature but have not yet been applied to the pediatric population (15-17). While this study was unable to determine the impact of timing of insertion of the temporary RVAD due to small patient numbers (n= 24), it is likely that delayed implantation contributes to the risk of mortality. This speculation requires further exploration in the pediatric population.

The most common cause of death in this study was multi-organ failure (36.8%) with bleeding events (15.8%) and neurological events (15.8%) being the next most commonly reported cause. These results are comparable to the overall PediMACS publication that examined the outcomes in both pulsatile and continuous flow pumps were multi-system organ failure (39%, n=11/28) accounted for the majority of deaths with neurological dysfunction being less common (14%, n=4/28) (18). The PediMACS registry also reported their outcomes with continuous flow devices but did not comment on the causes of death. However, they did examine the adverse event profile and found an overall low adverse event rate with the most frequent early adverse events being bleeding, infection, arrhythmias and rehospitalization (9). Neurological events were less common, occurring at a rate of 4.1 events per 100 patient-months of support in the first 3 months and this rate decreasing to 0.8 after the first 3 months. These numbers were similar to those reported in the adult analysis of INTERMACS. Therefore, our findings of the causes of death are not surprising given the above information and further study is required to figure out who the patients are that suffer from multi-system organ failure and whether there are risk factors to predict this unfortunate outcome.

The advantage of the adult continuous flow VADs and the interest in implanting them in children stems from the ability to discharge patients back into the community. While this is the ultimate goal, the conclusion of this and other studies is that only about half of patients are ever discharged on the device (8-10). The reasons are likely multi-factorial and not specially examined in this study. However, we anticipate that this number may change with time as a number of pediatric centers are moving towards the adult model of delaying transplant listing after LVAD implantation in order to allow for the improvement of end organ function and optimization of rehabilitation. In addition, with increasing experience, centers will become more comfortable managing patients in the community and allow for the possibility of destination therapy (19).

3.4.1 Study limitations

This study does have a number of limitations inherent to retrospective data collection. This study collected a limited data set in order to increase the response rate from practitioners and to ensure that all data fields were collected. All efforts were made to include the majority of centers that have implanted children with this type of device, as there is no mechanism through the company to determine the number of devices implanted over this time frame, we are unable to estimate the percentage of patients missing from this dataset. Given this was a voluntary survey there is the potential for selection bias but our survival results due align with the PediMACS report on continuous flow devices. VAD related morbidities were not collected, as the focus of this study was to look at survival outcomes and associated risk factors. Patient selection and management was up to the individual institution and therefore we cannot account for these differences within this study. In addition, this analysis focused on one type of continuous flow pump and may not reflect the results of axial flow continuous pumps. Despite these limitations, our study does represent the largest and most contemporary cohort of pediatric patients with continuous flow VAD in the literature and is the first study to focus on an international experience.

3.4.2 Conclusion

The use of the HeartWare HVAD® system in the pediatric population is associated with a low mortality and the majority of patients were supported to transplant by one year post implant. These positive results appear to be independent of geographical location and therefore, may be transferable to many centers. The need for a temporary right heart support is a risk factor for poor outcomes and further work is required in the pediatric population to predict these higher risk patients in order to allow for pre-op, intra-op and post-operative optimization of outcomes. While survival results are promising, further studies are needed to delineate the associated morbidities with this technology in the pediatric population

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3.6 Tables

Table 3.1: Clinical Characteristics at Implantation (n=205)

Characteristic	N	N (%) or Median (IQR)
Male	205	125 (61%)
Age at Implantation (yrs)	205	13.1 (9.8 - 15.8)
Weight (Kg)	205	42.0 (28.0 - 60.0)
Height (cm)	205	152.0 (132.0 - 167.0)
Body surface area (m^2)	205	1.34 (1.01 - 1.66)
Year of Implant	205	
2009-2011		18 (8%)
2012-2014		114 (56%)
2015-2016		73 (35%)
Presence and type of Congenital Heart Disease	205	
Biventricular		12 (5.6%)
Univentricular		11 (5%)
Presence and type of Cardiomyopathy	205	
Dilated		132 (64%)
Restrictive		6 (2.9%)
Hypertrophic		6 (3%)
LV non-compaction		8 (4%)
Arrhythmogenic RV dysplasia		2 (1%)
Other		8 (4%)
Biventricular CHD and Cardiomyopathy		6 (2.9%)
Other Diagnosis		14(6.8%)
Previous Sternotomy	205	47 (23%)
Pediatric Implantation Centre	205	
Non-pediatric implant center		14 (7%)
Pediatric implant center		190 (93%)
Type of VAD Implantation	205	
LVAD		189 (92.2%)
RVAD		1 (0%)
BiVAD		4 (2%)
Single Ventricle VAD		11 (5.46 %)
Temporary RVAD Support	204	24 (12%)

LV: left ventricle; RV: right ventricle; LVAD: left ventricular assist device; RVAD: right ventricular assist device; BiVAD: biventricular assist device; VAD: ventricular assist device

Table 3.2: Clinical Characteristics at Implant Dichotomized by BSA

		>1 m^2		≤1 m^2	
Clinical Characteristics at Implantation	N		N		P-value
Male	155	94 (60.6%)	50	32 (64.0%)	0.74
Median Age at implantation [IQR]	155	14.1 (12.0 – 16.0)	50	7.3 (6.0 – 9.1)	<0.001
Median Weight (kg) [IQR]	155	51.2 (37.5 – 65.0)	50	20.0 (18.0 – 24.0)	<0.001
Median Height (cm) [IQr]	155	162 (147– 170)	50	120 (109 – 125)	<0.001
Median Body surface area (m2) [IQR]	155	1.53 (1.25 – 1.76)	50	0.83 (0.76 – 0.90)	<0.001
Presence and type of Congenital Heart Disease	155		50		0.05
Biventricular		6(3.89%)		6 (12.0)%	
Univentricular		7 (4.5%)		4 (8.0%)	
Presence and type of Cardiomyopathy	155		50		0.08
Dilated		107(69.0%)		25 (50.0%)	
Restricted		3(1.9%)		3 (6%)	
Hypertrophic		4 (2.6%)		2(4.0%)	
LV non-compaction		5 (3.2%)		3 (6%)	
Arrthmogenic RV dysplasia		2 (1.3%)		0 (0.0%)	
Other Cardiomyopathy		7(4.5%)		1 (2%)	
Presence of Cardiomyopathy and CHD	155	4(3%)	50	2(4%)	0.64
Other Diagnosis	155	10(6.5%)		4(7.3%)	
Previous Sternotomy	155	27 (17.4%)	50	20 (40%)	0.002
Year of VAD Implantation	155		50		0.05
2009-2011		17 (11%)		1 (2%)	
2012-2014		78 (50.3%)		36 (72%)	
2015-2016		60 (38.7%)		13 (26%)	
World Region	155		50		0.59
North America		96 (61.9%)		27 (54.0%)	
Europe		39 (25.2%)		18 (36.0%)	
Other		20 (12.9%)		5 (10%)	
Pediatric Implantation Centre	154		50		0.39
Yes		141 (91.0%)		49 (98.0%)	
Type of VAD Implantation	155		50		0.70
LVAD		144 (92.9%)		45 (90.0%)	
RVAD		1 (0.6%)		0 (0.0%)	
BiVAD		3 (1.9%)		1 (2.0%)	
Single Ventricle VAD		7 (4.5%)		4 (8.0%)	
Temporary RVAD Support	155	17 (11.0%)	50	7 (14.0%)	0.61

LV: left ventricle; RV: right ventricle; VAD: ventricular assist device; LVAD: left ventricular assist device; RVAD: right ventricular assist device; BiVAD: biventricular assist device

Table 3.3: Cause-specific hazard regression for post-VAD mortality

Variable	HR [95% CI]	P-value
Temporary RVAD support	10.65 [2.53, 44.81]	0.001
Pump exchange	7.86 [1.80, 34.24]	0.006
Baseline clinical characteristics		
Male	0.430 [0.14, 1.29]	0.131
Age at implantation	1.10 [0.91, 1.34]	0.33
BSA >1 (vs. ≤1 m^2)	0.31 [0.053, 1.795]	0.19
Presence of congenital heart disease	0.28 [0.03, 2.50]	0.26
Prior sternotomy	1.32 [0.31, 5.66]	0.71
Cardiomyopathy [ref: no CM]		0.40
Dilated	0.57 [0.11, 2.84]	
Other	0.27 [0.04, 2.03]	
Site (North American vs. other)	1.93 [0.64, 5.87]	0.24
Year of implantation [ref: 2013 or before]		0.71
2014	1.74 [0.46, 6.61]	
2015 or after	1.32 [0.34, 5.12]	

Table 3.4: Time-varying cause-specific hazard regression for post-VAD cardiac transplant

Variable	HR [95% CI]	P-value
Temporary RVAD support	1.75 [0.62, 4.97]	0.29
Pump exchange	1.9 [0.68, 5.30]	0.22
Baseline clinical characteristics		
Male	1.05 [0.70, 1.56]	0.82
Age at implantation	1.00 [0.94, 1.07]	1.00
BSA >1 (vs. ≤1 m^2)	1.13 [0.60, 2.14]	0.71
Presence of congenital heart disease	0.56 [0.21, 1.49	0.25
Prior sternotomy	1.30 [0.69, 2.45]	0.41
Cardiomyopathy [ref: no CM]		0.38
Dilated	1.52 [0.68, 3.42]	
Other	1.14 [0.48, 2.71]	
Site (North American vs. other)	1.08 [0.74, 1.58]	0.70
Year of implantation [ref: 2013 or before]		0.26
2014	0.73 [0.46, 1.17]	
2015 or after	0.69 [0.42, 1.13]	

3.7 Figures

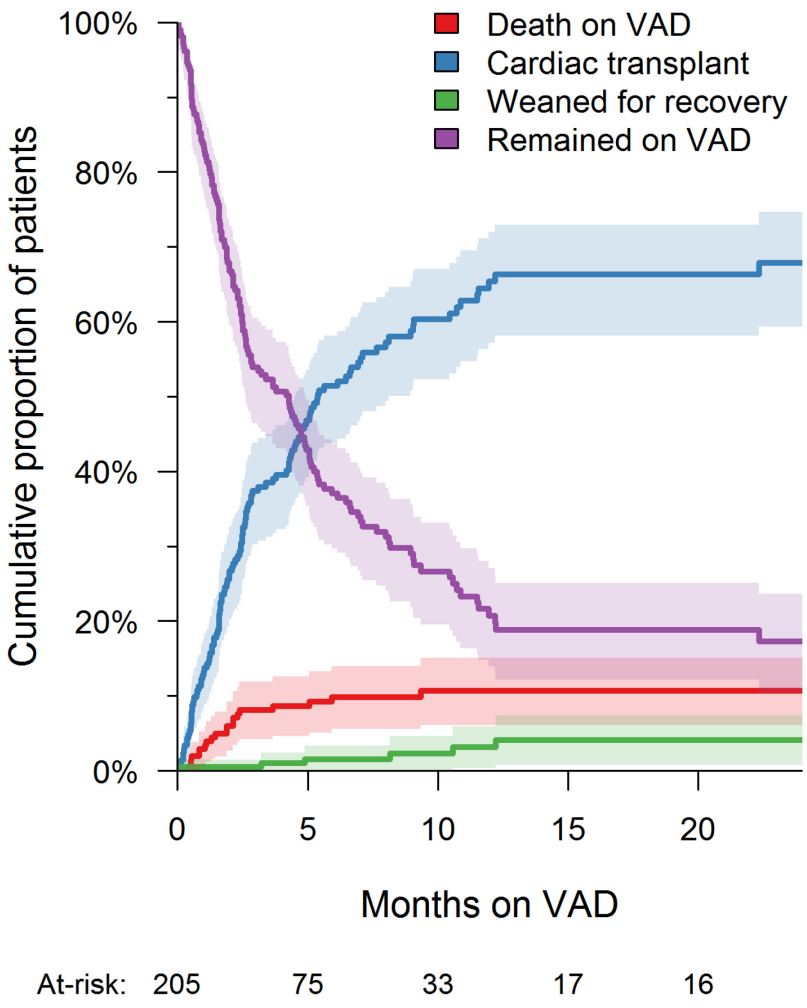

Figure 3.1: Competing outcome analysis following implantation of the HeartWare HVAD™.
The graphs show the proportion of patients who died, underwent transplant, remained on VAD support at any given month post implant. At 6 months post implant 51.5% were transplanted, 9.9% had died, 1.6% had been weaned for recovery and 37.1% remained on the VAD. By 12 months the proportion who underwent transplant was 65.4%, 10.7% had died, 3.2% weaned and 20.8% remained on the device.

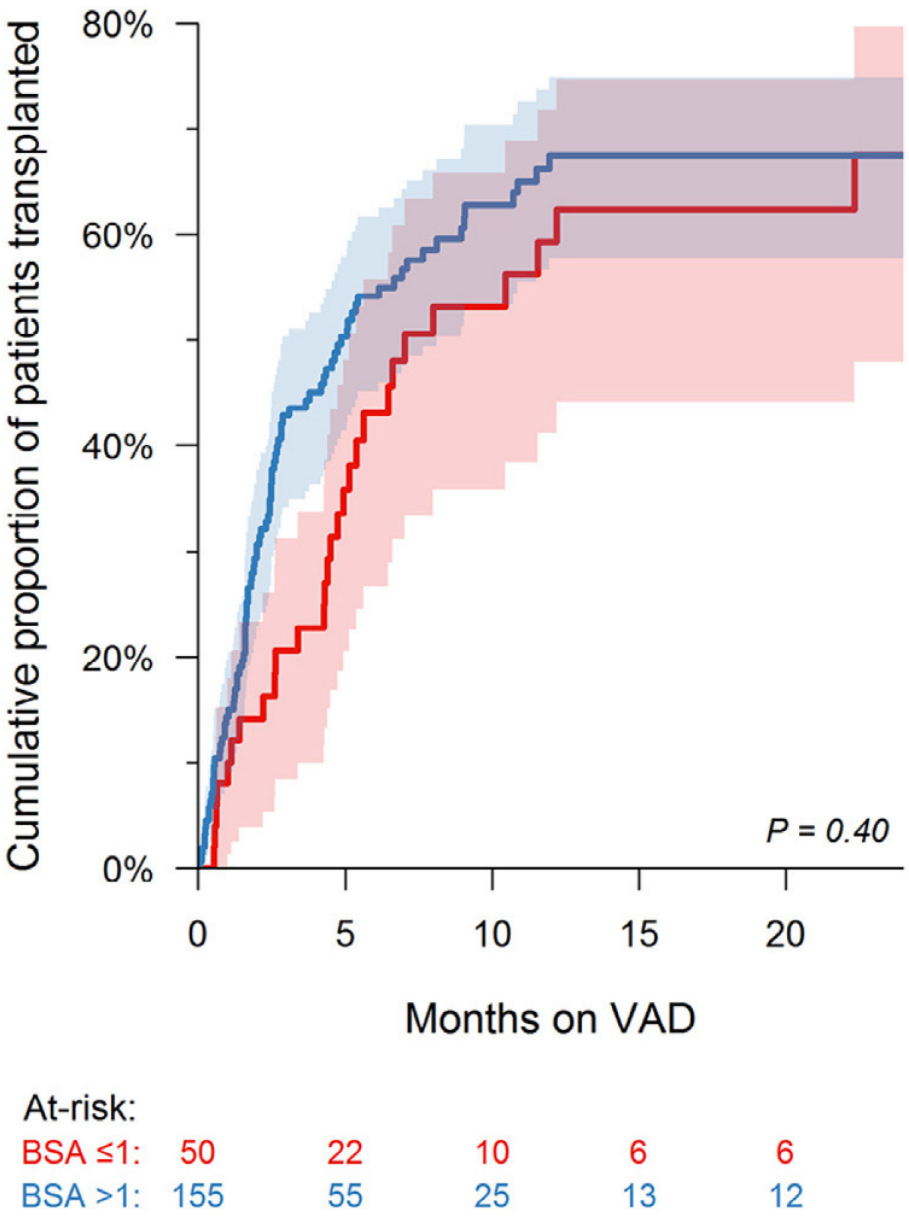

Figure 3.2: The cumulative proportion of patients who were transplanted from VAD support dichotomized by Body Surface Area (BSA)

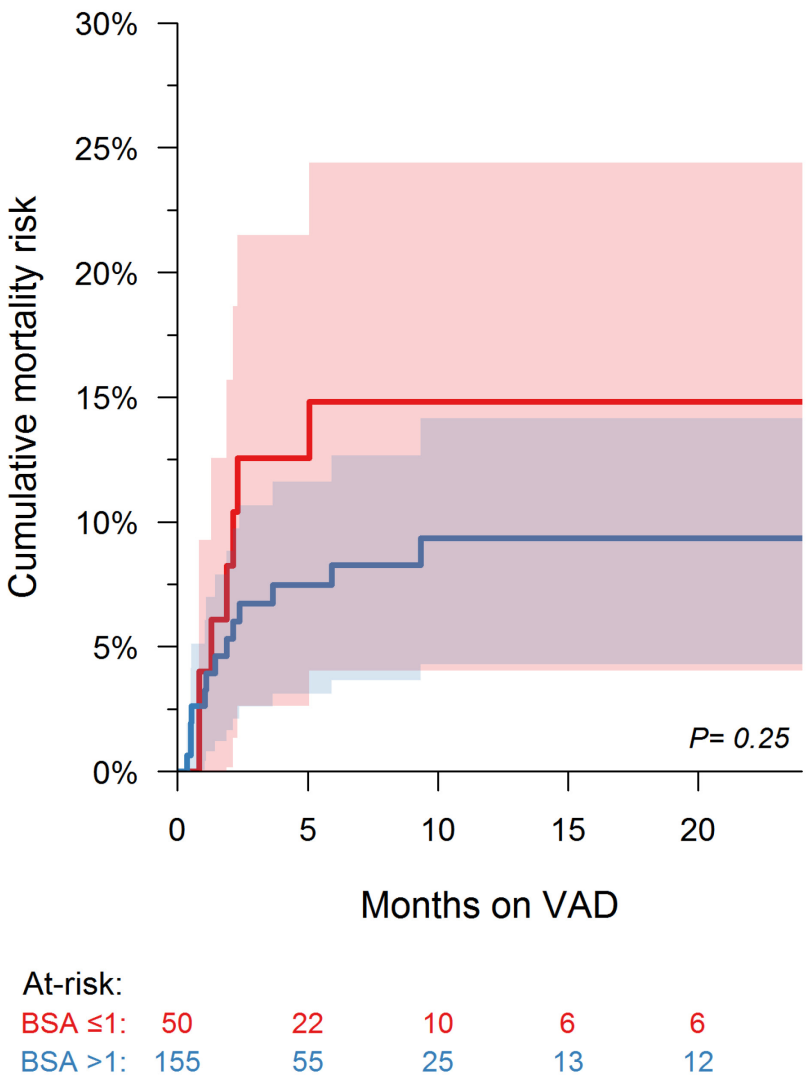

Figure 3.3: The cumulative proportion of patients who died on VAD support dichotomized by Body Surface Area (BSA).

At 12 months 14.8% (95th CI 4-24.4) in those with a BSA ≤1m^2 compared to 9.4% (95th CI 4.3-14.1%) (p=0.25).

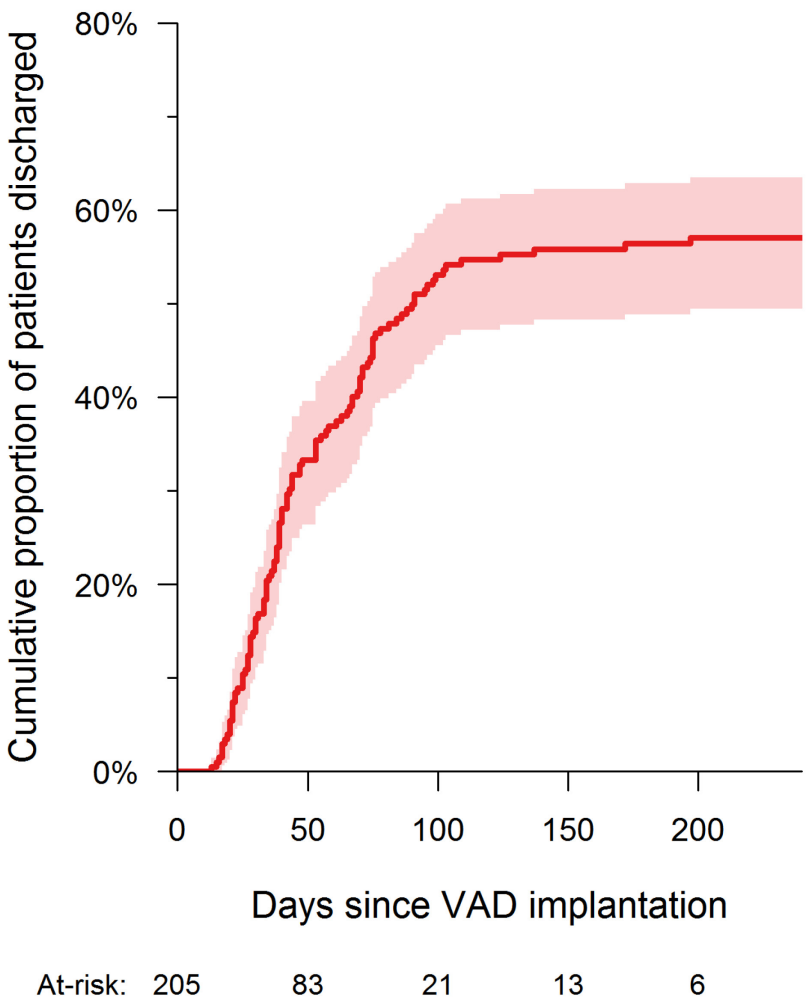

Figure 3.4: The cumulative proportion of patients discharged from hospital following VAD implantation

4 DISCUSSION, CLINICAL IMPLICATIONS, FUTURE RESEARCH DIRECTIONS, AND KNOWLEDGE TRANSLATION

Children with advanced heart failure unresponsive to medical management are the cohorts of patients where MCS is considered. The type of support chosen was limited in the past due to a lack of options for children. However, with the introduction of new devices there are now more options available. The type of MCS chosen depends on the indication for implant, the patient's size and underlying diagnosis. Yet, despite the increase in device types, there remain a number of controversies with regard to the best way to support the spectrum of children with advanced heart failure, due to the wide ranges of size and diagnosis for the patients. This thesis was designed to address some of these controversies with the aim to shed insight for practitioners that look after children with advanced heart failure.

4.1 Mechanical Circulatory Support in Children <10Kg

The first project was designed to assess if there was a superior modality of MCS for children <10Kg, given the known difficulties in supporting these patients. This study was a retrospective analysis of data that is prospectively collected within the Pediatric Heart Transplant Society's registry. This data has been collected over the last 25 years, and includes the majority of patients implanted in the United States, Canada and the United Kingdom. This study highlighted a number of interesting findings that are particularly relevant for clinical practice. Firstly, there is a difference in outcomes on MCS based on diagnosis in smaller children with those with cardiomyopathy fairing better than children with CHD regardless of the type of MCS that is first implanted. Secondly, for both cardiomyopathy and CHD patients, those implanted with a VAD as their first device as a bridge to transplant had better outcomes. Thirdly, children <5Kg were at greater risk of mortality, with those with CHD being particularly susceptible with no major difference in survival based on mode of support.

While these results highlight the importance of trying to understand the interactions between the device type and patients characteristics, the results may also reflect a potential bias in clinical practice based on patient characteristics and represent confounding by indication. It appears that ECMO, as a first line strategy, was primarily used in patients that were younger, smaller and in those with single ventricle physiology. These are all characteristics that have been identified as resulting in a difficult course following VAD therapy. For this reason, children <5Kg were left on ECMO for longer periods of time than would normally occur in clinical practice, likely secondary to the lack of available support options, therefore increasing the risk of mortality as time on device increased.

4.1.1 Strengths and Bias

Registry based research, such as this body of work, does have the advantage of being generalizable to the population due to the heterogeneous population of patients included. Despite the strong external validity there are a number of potential biases in the study design. This includes:

1) Information bias: Under reporting is a known risk when using data from a registry, especially when that data pertains to adverse events and mortality. The data in this first study was collected prospectively with regular adjudication with the hopes of mitigating under reporting.
2) Selection bias: There is no way to know if all patients at individual sites are included in the PTHS registry and therefore could result in a selection bias. In addition if a patient is transferred to another site they are lost to follow-up.

In addition to biases present it is possible that confounding could be present, as there may be risk factors that are associated with mortality that were not available and analyzed.

4.1.2 Implications for Future Research

To confirm these results a randomized control trial would be the optimal study design to answer the question as to which is the superior modality of support. However, given the complications associated with ECMO, the need to be intubated and ventilated and the inability to mobilize patients this would be unethical and would have little buy in from the pediatric cardiology community. A matched case control study may provide further information about outcomes for patients with pre-defined characteristics, given that there were a number of differences in patient characteristics in this study when patients were examined by diagnosis or type of first device chosen. In addition, a prospective cohort study designed specifically to examine mechanical circulatory support outcomes, regardless if a patient was listed for transplant may also provided further insight as the current study is biased towards children who meet criteria to be listed for transplant. Those that were too sick for listing or died prior to listing were not included in this study. Lastly, the results of this study highlight the need for mechanical circulatory support that is designed for the unique features of small children, especially those with congenital heart disease and those <5Kg.

4.1.3 Implications for Clinical Practice

This article highlights the unique differences in outcomes for smaller children with MCS with both the cardiomyopathy/myocarditis and congenital heart disease population who were supported on VAD, having improved compared to ECMO. This was not shown to be true for children <5Kg. However, what was reported is that children <5Kg with CM/myocarditis had improved outcomes compared to those congenital heart disease. Smaller children requiring MCS are a heterogeneous patient population where variations in size, diagnosis, clinical condition, and timing of implantation being important parameters to take into account when deciding on MCS strategy. Currently, in children with dilated cardiomyopathy (DCM)<10Kg with advanced heart failure, it is imperative to monitor them closely to determine the point

where they fail medical management and reach criteria for MCS initiation, as the sicker a child is going into MCS the worse their outcomes. If a child has met criteria, then VAD implantation would be the first choice for MCS. As shown above this is due to improved survival results when compared to ECMO. In addition, VAD therapy allows for mobilization, rehabilitation, self-ventilation, oral nutritional intake and discharge to the general ward. These steps are essential to decreasing fragility in this patient population and improving their post heart transplant outcomes. For children with DCM who present in cardiogenic shock and require immediate MCS than ECMO initiation would be the only option. However, following stabilization of the patient, transitioning off ECMO to VAD would be recommended for improved longer-term survival, and is supported by the results of this study. For children with congenital heart disease <10Kg who require MCS, VAD therapy was shown to be superior in the overall cohort compared to ECMO. Initiation of VAD therapy in children with congenital heart disease is challenging given the many different forms of CHD and the underlying cause of heart failure. Consideration of anatomy, the physiology and mechanism of failure is very important in determining the type of MCS support to offer. For VAD therapy there are two options used in children with CHD including, paracorporeal continuous and paracorpeal pulsatile devices. While, this study did not differ between the two options, there are some unique features to both that need to be considered and further work is required to explore the role of each of these devices in the CHD population. VAD support should be offered as first line support for patients with CHD and ventricular dysfunction whose anatomy is favourable. For CHD patients with other mechanism of failure, besides ventricular dysfunction, VAD support is unlikely to be helpful. ECMO is often used in cases of acute deterioration, following surgery due to failure to wean from bypass or in situations where both the heart and lungs require support. If a CHD patient is cannulated onto ECMO, than attempts should be made to wean ECMO or to consider transition to a VAD. The same principles on the limitation of ECMO in the CM population apply to the children with CHD.

4.2 Durable Intracorporeal VAD Use in Children

The second project was developed due to the lack of information on the outcomes of children implanted with this adult designed device. Beside clinical outcomes it was unclear where the lower weight limit was for implantation of this device and if children with a BSA that was smaller than recommended for implant (i.e.:< 1 m^2) would have similar outcomes to larger children. This was an international, multi-center retrospective study and to date remains the only larger scale international study on VAD implantation in children. The children implanted with this device were predominantly adolescents with the median age of 13 years and weight of 42Kg. However, a quarter of the patients were below the recommended BSA cut off value, with the smallest child weighing 10 Kg. In general, the patients had a positive outcome with 90% either undergoing transplant, device removal for recovery or remained on the device at 1-year post implant. The HeartWare HVAD system used in this international pediatric cohort was associated with low

mortality and successful bridge to transplant with right heart support and pump exchange associated with mortality

4.2.1 Strengths and Potential Biases/Limitations

This study does have a number of limitations inherent to retrospective data collection. This study collected a limited data set in order to increase the response rate from practitioners and to ensure that all data fields were collected. VAD related morbidities were not collected, as the focus of this study was to look at survival outcomes and associated risk factors. Patient selection and management was up to the individual institution and therefore we cannot account for these differences within this study. In addition, this analysis focused on one type of continuous flow pump and may not reflect the results of axial flow continuous pumps. Despite these limitations, this study does represent the largest and most contemporary cohort of pediatric patients with continuous flow VAD in the literature and is the first study to focus on an international experience.

1) Selection Bias

Selection bias is the bias introduced by the way that individuals for the study are selected and therefore don't represent the population you are interested in studying. This cohort was a convenience cohort and limited by the number of pediatric patients available worldwide to study. While this study captured the majority of centers that implant VADs in children, there would be some centers that did not respond to the initial invite to participate and therefore bias may have been introduced. However, given our results are similar to recently published studies were the data is prospectively collected, this bias is likely less of an issue (1,2). A randomized control study would be ideal to minimize this type of bias, however it would not be ethical to conduct such a study for this patient population.

2) Confounding

In our multivariate analysis, there are likely variables that were not collected that could be associated with mortality, and therefore confounding may be present. The amount of data collected on each patient was minimized to increase compliance with the data collection. This design may have resulted in confounding; therefore, a prospective cohort study may be a better way to determine other factors associated with mortality.

4.2.2 Implications for Future Research

Due to the life threatening nature of heart failure, it would be difficult to design a randomized trial for VAD therapy. Further studies would best come from a prospective cohort study. Starting in 2012, the Pedimacs registry started collecting data on children and adolescents implanted with a VAD (3). In 2019, a publication from the Pedimacs registry looking at the use of the Heartware HVAD was published. This

study, while based on children on in the United States, confirmed the results of our retrospective analysis. There were 192 patients <19 years of age implanted with this device and compared to an older cohort of patients age 19-30 who were collected through the adult equivalent registry. The median age of implant was 14.4 years with the youngest being 2.7 years. The average weight was 51.5 Kg (13.1-162.6 Kg and body surface area between 0.6-2.9 m^2). The median duration of support was 2.8 months (<1 day to 33.3 months). At 6 months, 59.2% had undergone transplant, 32.2% were alive on the device, 8.6% had died and no patient had the device removed for recovery. Forty-seven percent of patients were discharged home with 68.1% requiring readmission. This study, along with one from the Euromacs Registry (4), further helped to define the cohort of patients supported with a Heartware HVAD by shedding light on the complications rate. Due to the retrospective nature of the study presented in the thesis and the difficulty with defining adverse events this was not examined. These registries have provided a wealth of information about patients support on intracorporeal continuous flow devices and along with the current study have highlighted some areas that require further exploration. This includes further understanding the barriers to discharging a patient home, how to improve the complications that arise post VAD implant and exploring the outcomes of this device in unique patient populations, such as those with congenital heart disease. In addition, although the above study was able to show no difference in survival outcome when smaller and larger BSA was compared, further research is need to define the lower weight cut-off associated with increased risk of implant in the pediatric population.

4.2.3 Implications for Clinical Practice

The use of the Heartware HVAD device in children is considered off label. Initially, due to this labelling there was hesitation by practitioners to introduce this technology into their center. However, given this specific study and the recent registry reports, the Heartware HVAD is now a standard device choice for pediatric patients of the right size with end stage heart failure. While this device is designed for adults with a body surface area >1 m^2, this study, and others, have shown the use of this technology can be expanded to children ≤1 m^2 with the lower weight limit for implantation currently thought to be around around 15-20 Kg based on technical aspects of implantation and a recent study that reported both acceptable survival results and a favourable adverse event profile (1).

4.3 Conclusion

Based on the two studies included in this thesis it is clear that the pediatric heart failure population who require VAD therapy is very heterogeneous. This presents many challenges in studying these patients and translating research outcomes into clinical practice. The two studies highlight the differences in device strategies based on patient size and within each of these studies there is further delineation of the patient population. The results of the two studies provide important information for practitioners that will aide in decision making with respect to device strategy and counselling of families prior to implantation.

4.4 References

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